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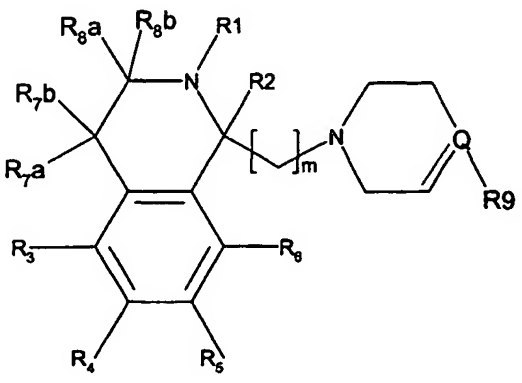
(54) Title: 3,4-DIHYDRO-1H-ISOQUINOLOIN-2-YL-DERIVATIVES



(I)

(57) Abstract: The present invention relates to novel compounds of formula I wherein the variable groups are as defined in the claims or a pharmaceutically acceptable acid addition salt thereof. The compounds of the invention are NK2 antagonists.

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3,4-dihydro-1H-isoquinolin-2-yl-derivatives

Field of the Invention

The compounds of the present invention belong to a novel class of 3,4-dihydro-1H-isoquinolin-2-yl-derivatives having affinity for the neurokinin 2 (NK2) receptor. The compounds are NK2-antagonists and are useful in the treatment of those diseases where an NK2-receptor is implicated like asthma and a CNS-disease. These novel 3,4-dihydro-1H-isoquinolin-2-yl-derivatives are capable of penetrating the blood brain barrier and therefore useful in treating a variety of CNS diseases.

Background of the invention

Three tachykinins, Substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) are widely distributed throughout the peripheral and central nervous systems. The biological effects of these neuropeptides are carried out via binding to their preferred receptors, NK1, NK2 and NK3 (Guard, S. and Watson, S. P. *Neurochem. Int.* **1991**, *18*, 149). Substance P displays highest affinity for the NK1 receptors, whereas NKA and NKB bind preferentially to NK2 and NK3 receptors, respectively. The selectivities of the endogenous ligands for their respective receptors are not absolute (reviewed in Regoli, D. et al. *Pharmacol. Rev.* **1994**, *46*, No. 4, 551 plus Bremer, A. A. et al. *Eur J Pharmacol* **2001**, *423*, 143). The three receptor subtypes belong to the G-protein-coupled receptor super family and have been cloned in various species including mice, rats and humans (Giardina, G. A. M. et al. *Drugs of the Future* **1997**, *22*, 1235 and references herein).

Activation of the tachykinin receptors influences a broad array of biological actions, including pain transmission, vasodilation, smooth muscle contraction, secretion of saliva, bronchoconstriction, activation of the immune system (inflammatory pain), neurogenic inflammation and neurotransmission (Patacchini, R. et Maggi, C.A. *Eur J Pharmacol.* **2001**, 429, 13; Longmore, J. et al. *Can J Physiol Pharmacol* **1997**, *75*, 612; Giardina, G. A. M. et al. *Drugs of the Future* **1997**, *22*, 1235 and references herein).

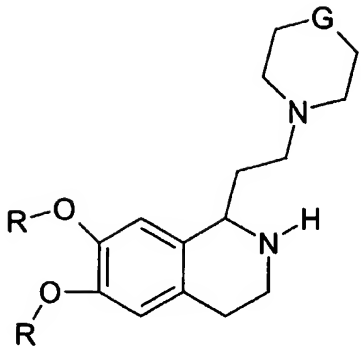
Expression of NK2 receptors in human is somewhat controversial. The receptor is generally expressed in low amounts in CNS, and autoradiographic studies have failed to show NK2 receptors in the human brain. A recent reverse transcription-polymerase chain reaction (RT-PCR) study, however, has revealed a detectable expression of NK2 receptor mRNA in various human brain regions including caudate nucleus, putamen, hippocampus, substantia nigra and cerebral cortex (Bensaid, M et al. *Neurosci Lett* **2001**, *303*, 25).

Up-regulation of the preprotachykinin (PPT) genes and mRNAs for the neurokinin receptors occurs both in animal models of disease (Fischer, A. et al. *J Clin Invest* **1996**, *98*, 2284) and in human diseases, such as asthma (Adcock, I. M. et al. *J Mol Endocrino* **1993**, *11*, 1).

NK antagonists have been and are under investigations for the treatment of a vast amount of both CNS related and peripheral diseases. A number of pre-clinical studies have been performed to assess the involvement of NK1 and NK2 receptors mediation and modulation of diseases related to anxiety and/or depression (Griebel, G. Et al. *Psycopharmacology*, **2001**, 158, 241; Walsh, D. M. et al. *Psychopharmacology* **1995**, *121*, 186; Rupniak, N. M. et al. *Neuropharmacology* **2000**, *39*, 1413; Rupniak, N. M. et Kramer, M.S. *TiPS* **1999**, 20, 485;; Giardina, G. A. M. et al. *Drugs of the Future* **1997**, *22*, 1235, and references in these).

These studies indicate that NK2 antagonists will be useful in treating or preventing a variety of brain disorders including depression, manic depression, bipolar disorder, dysthymia, mixed anxiety depression, generalised anxiety disorder, social anxiety disorder, panic anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, acute stress disorder, phobia, pre-menstrual dysphoric disorder, psychosis, and Huntington's disease as well as Parkinson's disease, adjustment disorders, pain, emesis, migraine, epilepsia, obesity, asthma and cerebrovascular disease. However, peripheral diseases such as inflammation, inflammatory bowel disease, hypertension, arthritis, cardiovascular diseases, neuritis, neuralgia, urticaria, incontinence, gastrointestinal diseases, influenza, allergy, pulmonary allergy and carcinoma / tumural growth may also be addressed by NK2 antagonists.

US 3,994,891 discloses tetrahydroisoquinolines of the general formula



wherein R is hydrogen or methyl, and G is NH or CH2. The dihydroxy compounds are described as effective vasodilators, whereas the dimethoxy compounds are intermediates in the manufacture of the dihydroxy compounds.

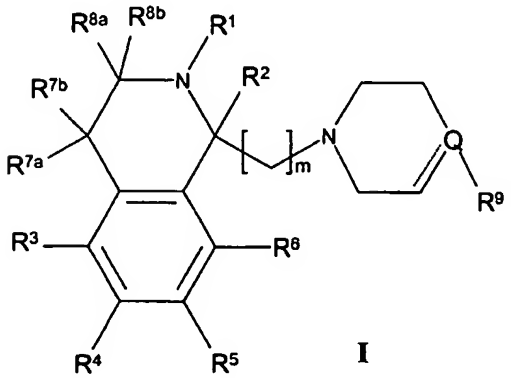
Hence, there is a desire for novel compounds that are antagonists at the NK2 receptor.

Summary of the Invention

The objective of the present invention is to provide compounds that are antagonists at the NK2 receptor.

A further objective of the present invention is to provide compounds with such activities which have improved solubility, metabolic stability and/or bioavailability compared to prior art compounds.

Accordingly, the present invention relates to novel compounds of formula I



I

wherein

R^1 is a group $R^{11}CO$-, $R^{11}CS$-, $R^{11}SO_2$-, $R^{11}OCO$-, $R^{11}SCO$- or $R^{11}CO$-$CR^{12}R^{13}$- wherein R^{11} is C_{1-12}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl, aryl-C_{1-6}-alkyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, tetrahydropyranyl, 1,2,3,4-tetrahydronaphtalenyl, or 4H-benzo[1,3]dioxinyl optionally substituted with halogen wherein each of said C_{1-6}-alkyl, aryl, heteroaryl and C_{3-8}-cycloalkyl groups independently are unsubstituted or substituted with one or more substituents selected from the group comprising halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, aryl-C_{1-6}-alkoxy, C_{1-6}-alkylsulfanyl, aryl and aryloxy wherein said aryl and aryloxy independently are unsubstituted or substituted with one or more halogen, and R^{12} and R^{13} independently are hydrogen or C_{1-6}-alkyl; or R^1 is a group $R^{14}R^{15}NCO$-, $R^{14}R^{15}NCS$-, wherein R^{14} and R^{15} are independently hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl or aryl-C_{1-6}-alkyl, wherein each of said C_{1-6}-alkyl, aryl and C_{3-8}-cycloalkyl groups independently are unsubstituted or substituted with one or more substituents selected from the group comprising halogen, C_{1-6}-alkyl and C_{1-6}-alkoxy, or R^{14} and R^{15} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepinyl group;

R^2 is selected from hydrogen, trifluoromethyl and C_{1-6}-alkyl;

R^3-R^6, R^{7a}, R^{7b}, R^{8a} and R^{8b} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl;

m is 2-6;

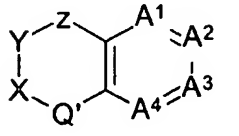
R^9 is benzyl, benzoyl, 2,3-dihydrobenzofuranyl or mono- or bicyclic aryl or heteroaryl wherein each benzyl, benzoyl, aryl or heteroaryl optionally is substituted with one or more substituents selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino,

C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl;

Q is C, N or CR^{10};

wherein R^{10} is selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoromethylsulfonyl, a group $-NR^{30}COR^{31}$ wherein R^{30} is hydrogen or C_{1-6}-alkyl and R^{31} is C_{1-6}-alkyl, a group $-COOR^{16}$ wherein R^{16} is hydrogen or C_{1-6}-alkyl, or a group $-CONR^{17}R^{18}$ wherein R^{17} and R^{18} independently are selected from hydrogen and C_{1-6}-alkyl or R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is unsubstituted or substituted with a C_{1-6}-alkyl;

or R^9 and R^{10} together with the carbon to which they are attached form a cyclic structure selected from the group comprising:



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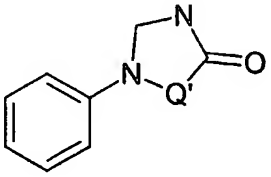

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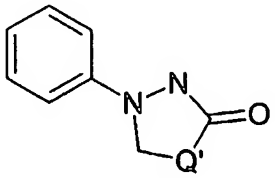

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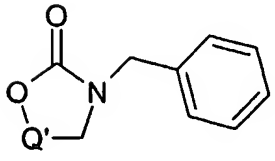


4)

wherein Q' is the carbon shared with the piperidine ring, so that said cyclic structure together with said piperidine ring form a spiro structure; and

X, Y, and Z are independently chosen from O; NR^{19}; $CR^{23}R^{24}$; $S(O)_n$ and a bond; wherein R^{19} is selected from hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, trifluoromethyl, acyl, thioacyl and trifluoromethylsulfonyl, or R^{19} is a group $R^{20}SO_2$-, $R^{20}OCO$- or $R^{20}SCO$- wherein R^{20} is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, or R^{19} is a group $R^{21}R^{22}NCO$- or $R^{21}R^{22}NCS$-, wherein R^{21} and R^{22} are independently hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, or aryl, wherein said aryl is unsubstituted or substituted with one or more substituents selected from C_{1-6}-alkyl or halogen; or R^{21} and R^{22} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepinyl group; R^{23} and R^{24} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl, heteroaryl, wherein said aryl is unsubstituted or substituted with one or more substituents selected from C_{1-6}-alkyl or halogen, amino, C_{1-6}-alkylamino, a group $NR^{25}R^{26}$ wherein R^{25} and R^{26} are independently selected from C_{1-6}-alkyl C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl or R^{25} and R^{26} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl or morpholinyl group, or R^{23} and R^{24} together is oxo; and n is 0, 1 or 2; provided that no more than one of X, Y and Z may be a bond, and provided that two adjacent groups X, Y or Z may not at the same time be selected from O and S; and

A^1, A^2, A^3 and A^4 are independently selected from N and CR^{27} wherein R^{27} is hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoromethylsulfonyl C_{1-6}-alkylsulfonyl amino or a group $NR^{28}R^{29}$ wherein R^{28} and R^{29} are independently selected from hydrogen and C_{1-6}-alkyl or R^{28} and R^{29} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl or morpholinyl group; provided that only one of A^1, A^2, A^3 and A^4 may be N; and

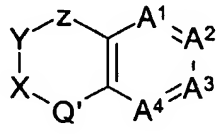
the dotted line emanating from Q is a bond when Q is C, and no bond when Q is CR^{10} or N;

or a pharmaceutically acceptable acid addition salt thereof.

Detailed Description of the Invention

The C_{1-12}-alkyl groups defined for R^{11} are preferably selected from C_{1-10}-alkyl, more preferred C_{1-8}-alkyl, and most preferred C_{3-8}-alkyl.

In one embodiment, the present invention relates to such compounds wherein Q is CR^{10}, and R^9 and R^{10} together with the carbon to which they are attached form a bicyclic structure:



1),

wherein Q' is the carbon shared with the piperidine ring, so that said bicyclic structure together with said piperidine ring form a spiro structure; and

X, Y and Z are independently chosen from O; NR^{19}; $CR^{23}R^{24}$ and $S(O)_n$ wherein R^{19} is selected from hydrogen, $C1_{-6}$-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, trifluoromethyl, acyl, thioacyl and trifluoromethylsulfonyl, or R^{19} is a group $R^{20}SO_2$-, $R^{20}OCO$- or $R^{20}SCO$- wherein R^{20} is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, or R^{19} is a group $R^{21}R^{22}NCO$-, $R^{21}R^{22}NCS$-, wherein R^{21} and R^{22} are independently hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, wherein said aryl is unsubstituted or substituted with one or more substituents selected from C_{1-6}-alkyl or halogen; or R^{21} and R^{22} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepinyl group; R^{23} and R^{24} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl, heteroaryl, wherein said aryl is unsubstituted or substituted with one or more substituents selected from C_{1-6}-alkyl or halogen, amino, C_{1-6}-alkylamino, a group $NR^{25}R^{26}$ wherein R^{25} and R^{26} are independently selected from C_{1-6}-alkyl or R^{25} and R^{26} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl or morpholinyl group, C_{1-6}-alkylcarbonyl, aminocarbonyl,

C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl, and C_{1-6}-alkylsulfonyl or R^{23} and R^{24} together is oxo; and n is 0, 1 or 2; and a bond; provided that no more than one of X, Y and Z may be a bond, and provided that two adjacent groups X, Y or Z may not at the same time be selected from O and S; and

A^1, A^2, A^3 and A^4 are independently selected from N and CR^{27} wherein R^{27} is hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, a group $NR^{28}R^{29}$ wherein R^{28} and R^{29} are independently selected from hydrogen and C_{1-6}-alkyl or R^{28} and R^{29} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl or morpholinyl group, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoromethylsulfonyl or C_{1-6}-alkylsulfonyl; provided that only one of A^1, A^2, A^3 and A^4 may be N.

In a preferred embodiment, the present invention relates to such compounds wherein X, Y and Z are selected from one of the combinations: X is oxygen, Y is a bond and Z is $CR^{23}R^{24}$; X is $CR^{23}R^{24}$, Y is a bond and Z is oxygen; X is NR^{19}, Y is a bond and Z is $CR^{23}R^{24}$; X is $CR^{23}R^{24}$, Y is a bond and Z is NR^{19}; X is CO, Y is a bond and Z is NR^{19}; X is SO_2, Y is a bond and Z is NR^{19}; X is SO, Y is a bond and Z is NR^{19}; X is $CR^{23}R^{24}$, Y is a bond and Z is S; X is $CR^{23}R^{24}$, Y is a bond and Z is SO; X is $CR^{23}R^{24}$, Y is a bond and Z is SO_2; wherein R^{19} is hydrogen, acetyl or methylsulfonyl and R^{23} and R^{24} are independently selected from hydrogen, methyl, isobutyl, cyclohexyl and 4-fluorophenyl.

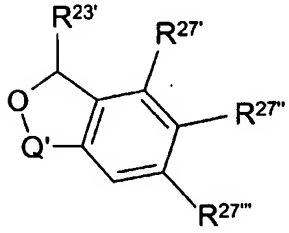
In another preferred embodiment, the present invention relates to such compounds wherein -X-Y-Z- together form a group selected from: -O-$CR^{23}R^{24}$-, -$CR^{23}R^{24}$-O-, -NR^{19}-$CR^{23}R^{24}$-, -$CR^{23}R^{24}$-NR^{19}-, -CO-NR^{19}-, -SO_2-NR^{19}-, -SO-NR^{19}-, -$CR^{23}R^{24}$-S-, -$CR^{23}R^{24}$-SO-, -$CR^{23}R^{24}$-SO_2-; wherein R^{19} is hydrogen, acetyl or methylsulfonyl tyl and R^{23} and R^{24} are independently selected from hydrogen, methyl, isobutyl, cyclohexyl and 4-fluorophenyl.

In another preferred embodiment, the present invention relates to such compounds wherein A^3 is N or CR^{27} wherein R^{27} is halogen, cyano, nitro, a group $NR^{28}R^{29}$ wherein R^{28} and R^{29}

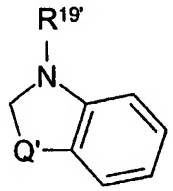
are independently selected from hydrogen and C_{1-6}-alkyl or R^{28} and R^{29} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl or morpholinyl group, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoromethylsulfonyl or C_{1-6}-alkylsulfonyl.

In another preferred embodiment, the present invention relates to such compounds wherein A^1, A^2, A^3 and A^4 are independently selected from CR^{27} wherein R^{27} is as defined above.

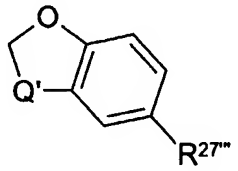
In a more preferred embodiment, the present invention relates to such compounds wherein bicyclic structure described above is selected from the group comprising:



a)



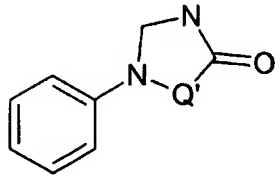
b)



c)

wherein $R^{19'}$ is acetyl or methylsulfonyl, $R^{23'}$ is hydrogen or methyl, $R^{27'}$ is hydrogen or fluoro, $R^{27''}$ is hydrogen, fluoro, methyl or isopropyl, $R^{27'''}$ is hydrogen, fluoro or trifluoromethyl.

In another embodiment, the present invention relates to such compounds wherein R^9 and R^{10} together with the carbon to which they are attached form a cyclic structure selected from the group comprising:



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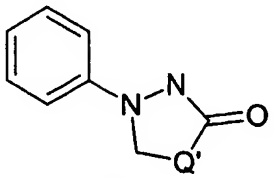

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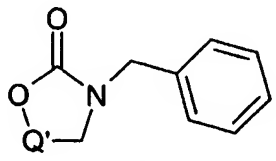


4)

wherein Q' is the carbon shared with the piperidine ring, so that said cyclic structure together with said piperidine ring form a spiro structure

In yet another embodiment, the present invention relates to such compounds wherein R^9 is benzyl, benzoyl, 2,3-dihydrobenzofuran-7-yl or mono- or bicyclic aryl or heteroaryl wherein each benzyl, benzoyl, aryl or heteroaryl optionally is substituted with one or more substituents selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C1$_{-6}$-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl.

In yet another embodiment, the present invention relates to such compounds wherein R^9 is 2,3-dihydrobenzofuran-7-yl, benzyl or benzoyl wherein said benzyl or benzoyl is unsubstituted or substituted with one or more halogens in the phenyl groups, or R^9 is mono- or bicyclic aryl or heteroaryl selected from the group comprising phenyl, indolyl, pyridyl, thiophenyl and benzisoxazolyl, wherein each aryl or heteroaryl optionally is substituted with one or more substituents selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C1$_{-6}$-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl.

In a preferred embodiment, the present invention relates to such compounds wherein said mono- or bicyclic aryl or heteroaryl is selected from the group comprising phenyl, indol-3-yl and benzisoxazol-3-yl wherein said phenyl, indol-3-yl or benzisoxazol-3-yl optionally is substituted with one or more substituents selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C1$_{-6}$-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl.

In an even more preferred embodiment, the present invention relates to such compounds wherein said optional substituents are selected from the group comprising halogen, phenyl and methyl.

In yet another embodiment, the present invention relates to such compounds wherein Q is CR^{10} wherein R^{10} is selected from hydrogen, C_{1-6}-alkylcarbonyl, hydroxy, a group $-NR^{30}COR^{31}$ wherein R^{30} is hydrogen or C_{1-6}-alkyl and R^{31} is C_{1-6}-alkyl, a group $-COOR^{16}$ wherein R^{16} is C_{1-6}-alkyl, or a group $-CONR^{17}R^{18}$ wherein R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl are unsubstituted or substituted with a C_{1-6}-alkyl.

In a preferred embodiment, the present invention relates to such compounds wherein R^{10} is selected from hydrogen, acetyl, hydroxy, a group $-NR^{30}COR^{31}$ wherein R^{30} is hydrogen and R^{31} is methyl, a group $-COOR^{16}$ wherein R^{16} is ethyl, or a group $-CONR^{17}R^{18}$ wherein R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl or a 4-methylpiperazinyl.

In another preferred embodiment, the present invention relates to such compounds wherein m is 2,3 or 4, more preferred m is 2.

In yet another embodiment, the present invention relates to such compounds wherein R^1 is a group $R^{11}CO$-, $R^{11}OCO$- wherein R^{11} is C_{3-6}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, phenyl, phenyl-C_{1-6}-alkyl, pyridyl, furanyl, benzo[1,2,5]oxadiazolyl, quinoxalinyl, benzo[b]thiophenyl or naphthalenyl wherein each of said C_{3-6}-alkyl, phenyl, pyridyl and furanyl groups independently are unsubstituted or substituted with one or more substituents selected from the group comprising halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, phenyl and phenoxy wherein said phenyl and phenoxy independently are unsubstituted or substituted with one halogen; or R^1 is a group $R^{14}R^{15}NCO$-, wherein R^{14} and R^{15} are independently hydrogen, C_{1-6}-alkyl, aryl, or aryl-C_{1-6}-alkyl, wherein each of said C_{1-6}-alkyl and aryl groups independently are unsubstituted or substituted with one substituent selected from the group comprising halogen and C_{1-6}-alkoxy.

In yet another embodiment, the present invention relates to such compounds wherein R^2 is hydrogen.

In yet another embodiment, the present invention relates to such compounds wherein R^3 is hydrogen.

In yet another embodiment, the present invention relates to such compounds wherein R^4 is hydrogen or methoxy.

In yet another embodiment, the present invention relates to such compounds wherein R^5 is hydrogen or methoxy.

In yet another embodiment, the present invention relates to such compounds wherein R^6 is hydrogen.

In yet another embodiment, the present invention relates to such compounds wherein R^{7a} and R^{7b} is hydrogen.

In yet another embodiment, the present invention relates to such compounds wherein R^{8a} and R^{8b} is hydrogen.

Preferred compounds of the invention are compounds number 1-209 as disclosed in the experimental section as well as the compounds in the following list:

1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone,

1-cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

N-[1-{2-[2-(1-cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

1-cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro *1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone,

1-(1-{2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(cyclopentyl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-(4-fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-cyclopentyl-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone,

1-cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

N-[1-{2-[2-(1-cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

1-cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl}methanone,

1-(4-fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl}methanone,

1-cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro *1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl}methanone,

1-(4-fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl}methanone,

1-cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone,

1-(1-{2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-1-(cyclopentyl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-methanone,

1-(4-fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-methanone,

1-cyclopentyl-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone,

1-cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

N-[1-{2-[2-(1-cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

1-cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro *1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone,

1-(1-{2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(cyclopentyl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-(4-fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-cyclopentyl-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone,

1-cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

N-[1-{2-[2-(1-cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

1-cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro *1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone,

1-(1-{2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(cyclopentyl)methanone,

1-(4-fluorophenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-(4-fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-cyclopentyl-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone, and

1-cyclopentyl-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone.

The compounds of the invention are NK_2 receptors antagonists having a human NK_2 binding affinity (IC50) of 5 μM or less, typically of 1 μM or less, preferably of 200 nM or less, more preferred of 50 nM or less and most preferred of 10 nM or less.

Accordingly, the compounds of the invention are considered useful in treating a variety of CNS diseases such as depression, manic depression, bipolar disorder, dysthymia, mixed anxiety depression, generalised anxiety disorder, social anxiety disorder, panic anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, acute stress disorder, phobia, pre-menstrual dysphoric disorder, psychosis and Huntington's disease as well as Parkinson's dementia, adjustment disorders, pain, emesis, migraine, epilepsia, obesity and cerebrovascular disease.

In particular, the compounds of the invention are considered useful in the treatment of depression, manic depression, bipolar disorder, dysthymia, mixed anxiety depression, generalised anxiety disorder, social anxiety disorder, panic anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, acute stress disorder, phobia, pre-menstrual dysphoric disorder and psychosis.

Thus, in another aspect, the present invention provides a pharmaceutical composition comprising at least one compound of formula I as defined above or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.

In a further aspect, the present invention provides the use of a compound of formula I as defined above or an acid addition salt thereof for the manufacture of a pharmaceutical preparation for the treatment of the above mentioned disorders.

The compounds of the general formula I may exist as optical isomers thereof and such optical isomers are also embraced by the invention. Throughout the specification and claims, reference to specific compounds refers to the racemates unless otherwise indicated.

The term C_{1-6}-alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, and 2-methyl-1-propyl. The terms C_{1-8}-alkyl, C_{1-10}-alkyl and C_{1-12}-alkyl, respectively, refer similarly to branched or unbranched alkyl group having from one to eight, ten or twelve carbon atoms inclusive, respectively.

Similarly, C_{2-6}-alkenyl and C_{2-6}-alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond, respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The term C_{3-8}-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, etc.

Halogen means fluoro, chloro, bromo or iodo.

As used herein, the term acyl refers to a formyl, C_{1-6}-alkylcarbonyl, arylcarbonyl, aryl-C_{1-6}-alkylcarbonyl, C_{3-8}-cycloalkylcarbonyl or a C_{3-8}-cycloalkyl-C_{1-6}-alkyl-carbonyl group, and the term thioacyl is the corresponding acyl group, in which the carbonyl group is replaced with a thiocarbonyl group.

The terms C_{1-6}-alkoxy, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylamino, C_{1-6}-alkylcarbonyl, and the like, designate such groups in which the C_{1-6}-alkyl and the C_{3-8}-cycloalkyl group are as defined above.

The term aryl refers to a carbocyclic aromatic group, such as phenyl or naphthyl, in particular phenyl.

The term heteroaryl refers to 5-membered monocyclic rings such as 1*H*-tetrazolyl, 3*H*-1,2,3-oxathiazolyl, 3*H*-1,2,4-oxathiazolyl, 3*H*-1,2,5-oxathiazolyl, 1,3,2-oxathiazolyl, 1,3,4-oxathiazolyl, 1,4,2-oxathiazolyl, 3*H*-1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,4,2-dioxazolyl, 3*H*-1,2,3-dithiazolyl, 3*H*-1,2,4-dithiazolyl, 1,3,2-dithiazolyl, 1,4,2-dithiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1*H*-imidazolyl, 1*H*-pyrazolyl, 1*H*-pyrrolyl, furanyl, thienyl, 1*H*-pentazole; 6-membered monocyclic rings such as 1,2,3-oxathiazinyl, 1,2,4-oxathiazinyl, 1,2,5-oxathiazinyl, 4*H*-1,3,5-oxathiazinyl, 1,4,2-oxathiazinyl, 1,4,3-oxathiazinyl, 1,2,3-dioxazinyl, 1,2,4-dioxazinyl, 4*H*-1,3,2-dioxazinyl, 4*H*-1,3,5-dioxazinyl, 1,4,2-dioxazinyl, 2*H*-1,5,2-dioxazinyl, 1,2,3-dithiazinyl, 1,2,4-dithiazinyl, 4*H*-1,3,2-dithiazinyl, 4*H*-1,3,5-dithiazinyl, 1,4,2-dithiazinyl, 2*H*-1,5,2-dithiazinyl, 2*H*-1,2,3-oxadiazinyl, 2*H*-1,2,4-oxadiazinyl, 2*H*-1,2,5-oxadiazinyl, 2*H*-1,2,6-oxadiazinyl, 2*H*-1,3,4-oxadiazinyl, 2*H*-1,3,5-oxadiazinyl, 2*H*-1,2,3-thiadiazinyl, 2*H*-1,2,4-thiadiazinyl, 2*H*-1,2,5-thiadiazinyl, 2*H*-1,2,6-thiadiazinyl, 2*H*-1,3,4-thiadiazinyl, 2*H*-1,3,5-thiadiazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 2*H*-1,2-oxazinyl, 2*H*-1,3-oxazinyl, 2*H*-1,4-oxazinyl, 2*H*-1,2-thiazinyl, 2*H*-1,3-thiazinyl, 2*H*-1,4-thiazinyl, pyrazinyl, pyridazinyl, pyrimidyl, pyridyl, 2*H*-pyranyl, 2*H*-thiinyl; and to bicyclic rings such as 3*H*-1,2,3-benzoxathiazolyl, 1,3,2-benzodioxazolyl, 3*H*-1,2,3-benzodithiazolyl, 1,3,2-benzodithiazolyl, benzfurazanyl, 1,2,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, 1*H*-benzotriazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, benzoxazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzothiazolyl, 1*H*-benzimidazolyl, 1*H*-indazolyl, 3*H*-1,2-benzoxathiolyl, 1,3-benzoxathiolyl, 3*H*-2,1-benzoxathiolyl, 3*H*-1,2-benzodioxolyl, 1,3-benzodioxolyl 3*H*-1,2-benzodithiolyl, 1,3-benzodithiolyl, 1*H*-indolyl, 2*H*-isoindolyl, benzofuranyl, isobenzofuranyl, 1-benzothienyl, 2-benzothienyl, 1*H*-2,1-benzoxazinyl, 1*H*-2,3-benzoxazinyl, 2*H*-1,2-benzoxazinyl, 2*H*-1,3-benzoxazinyl, , 2*H*-1,4-benzoxazinyl, 2*H*-3,1-benzoxazinyl, 1*H*-2,1-benzothiazinyl, 1*H*-2,3-benzothiazinyl, 2*H*-1,2-benzothiazinyl, 2*H*-1,3-benzothiazinyl, 2*H*-1,4-benzothiazinyl, 2*H*-3,1-benzothiazinyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, isoquinolyl,

quinolyl, 1*H*-2-benzopyranyl, 2*H*-1-benzopyranyl, 1*H*-2-benzothiopyranyl or 2*H*-1-benzothiopyranyl.

The acid addition salts of the compounds of the invention are pharmaceutically acceptable salts formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

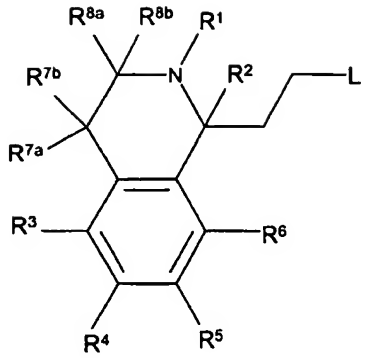
The pharmaceutical compositions of this invention, or those which are manufactured in accordance with this invention, may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 100 mg.

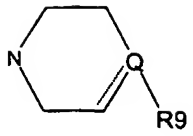
The total daily dose is usually in the range of about 0.05 - 500 mg, and most preferably about 0.1 to 50 mg of the active compound of the invention.

The compounds of the invention may be prepared as follows:

1) Alkylating a piperazine, piperidine or tetrahydropyridine of formula III with an alkylating derivative of formula II:



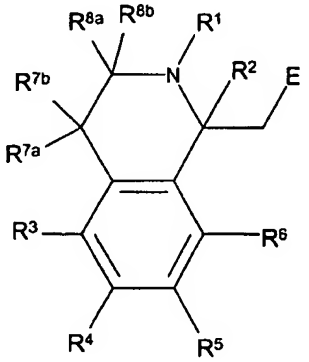
(II)



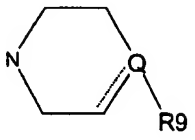
(III)

wherein R^1-R^9 and Q are as previously defined and L is a leaving group such as e.g. halogen, mesylate or tosylate;

2) Reductive alkylation of an amine of formula III with a reagent of formula IV:



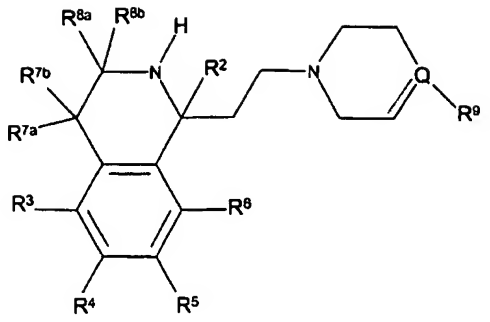
(IV)



(III)

wherein R^1-R^9 and Q are as previously defined and E is an aldehyde or an activated carboxylic acid;

3) Acylating an amine of formula V by the use of a carboxylic acid and a coupling reagent, an activated ester, an acid chloride, an isocyanate, carbamoyl chloride or by a two-step procedure by treatment with phosgene followed by addition of an amine:



(V)

wherein R^1-R^9 and Q are as previously defined, whereupon the compound of formula I is isolated as the free base or a pharmaceutically acceptable acid addition salt thereof.

The alkylation according to method 1) is conveniently performed in an organic solvent such as a suitably boiling alcohol or ketone, preferably in the presence of an organic or inorganic base (potassium carbonate, diisopropylethylamine or triethylamine) at reflux temperature. Alternatively, the alkylation can be performed at a fixed temperature, which is different from the boiling point, in one of the above-mentioned solvents or in dimethyl formamide (DMF), dimethylsulfoxide (DMSO), or N-methylpyrrolidin-2-one (NMP), preferably in the presence of a base. The alkylating agents of formula II can be prepared by methods analogues to those described in the examples or can be synthesised by applying methods described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York, namely under reaction conditions such as those which are known and suitable for such reactions. The amines of formula III are either commercially available or have been described in the literature or can be prepared by methods analogues to those described in the literature e.g. Marxer et al. *J. Org. Chem.* **1975**, *40*, 1427, by Parham et al. *J. Org. Chem.* **1976**, *41*, 2628 and by Bauer et al. *J. Med. Chem.* **1976**, *19*, 1315, Maligres et al. *Tetrahedron* 1997, 53, 10983, and by Cheng et al. *Tet. Lett.* 1997, 38, 1497, Chen, Meng-Hsin; Abraham, John A. *Tetrahedron Lett.* **1996**, *37*, 5233-5234 and Slade, P.D. et al. *J. Med. Chem.* **1998**, *41*, 1218-1235, or can be synthesised by methods described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John

Wiley & Sons, Inc. New York, namely under reaction conditions such as those which are known and suitable for such reactions.

The reductive alkylation according to method 2) is performed by standard literature methods or as described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York, namely under reaction conditions such as those which are known and suitable for such reactions. The reaction can be performed in two steps, e.g. coupling of amines of formula III with a reagent of formula IV by standard methods *via* the carboxylic acid chloride, activated esters or by the use of carboxylic acids in combination with a coupling reagents such as e.g. dicyclohexyl carbodiimide, followed by reduction of the resulting amide with lithium aluminium hydride or alane. The carboxylic acids of formula IV are either commercially available or can be prepared by methods analogues to those described in the literature (e.g. *Tet. Lett. 37*, **1996**, pp. 5453-5456; *Tet. Lett. 35*, **1994**, pp. 6567-6570; *J. Med. Chem. 25*, **1982**, pp. 1235-1240; *Synthesis* **1987**, pp. 474-477).

The acylation according to method 3) is conveniently performed by standard methods *via* the carboxylic acid chloride, activated esters or by the use of carboxylic acids in combination with coupling reagents such as e.g. dicyclohexyl carbodiimide. When the acylating reagent is carbamoyl chlorides or isocyanates, the acylation produces urea derivatives. The urea derivatives can also be prepared by a two-step procedure consisting of treatment with phosgene followed by addition of an amine.

The intermediate compounds of formula V are prepared as described in methods 1) and 2), wherein R^2-R^9, Q, L and E are as previously defined, and R^1 is a protection group. This protection group may be chosen from those protection group generally used for protection of amino groups. Those skilled in the art will know to select appropriate protection groups and how to protect and deprotect the amines with these protection groups.

Experimental Section

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with

IonSpray source and Shimadzu LC-8A/SLC-10A LC system. The LC conditions (C18 column 4.6 × 30 mm with a particle size of 3.5 µm) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 4 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times, R_t, are expressed in minutes.

Mass spectra were obtained by an alternating scan method to give molecular weight information. The molecular ion, MH+, was obtained at low orifice voltage (5-20V) and fragmentation at high orifice voltage (100-200V).

Preparative LC-MS-separation was performed on the same instrument. The LC conditions (C18 column 20 × 50 mm with a particle size of 5 µm) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (5:95:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet. NMR signals corresponding to acidic protons are generally omitted. For column chromatography silica gel of type Kieselgel 60, 230-400 mesh ASTM was used. For ion-exchange chromatography (SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat. No. 220776) was used. Prior use of the SCX-columns was pre-conditioned with 10% solution of acetic acid in methanol (3 mL).

Preparation of intermediates

Alkylating reagents of the formula II

1. *(RS)-1-(2-Bromo-ethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid-tert-butyl ester*
Tetrahydrosioquinolinic acid (10 g) was suspended in tetrahydrofuran THF (100 mL). Triethyl amine (9.1 mL) and di-tert-butyl dicarbonate (14.3 g) was added and the mixture stirred at room temperature for 16 h. The mixture was concentrated *in vacuo*, redissolved in ethyl acetate (250 mL) and washed twice with and aqueous 0.5 M KHSO4-solution (200 mL), dried over magnesium sulphate and evaporated *in vacuo* to give 1-carboxymethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester in quantitative yield as a clear oil which crystallised upon standing. The protected amino acid was dissolved in dry tetrahydrofuran under nitrogen, cooled to 0 °C and 1M borane in tetrahydrofuran (41.5 mL) was added slowly under nitrogen during 15 min. The mixture was warmed to room temperature and stirred for 1h. Excess borane was carefully destroyed by slow addition of 50 mL of a 1:1 mixture of water/tetrahydrofuran. The mixture was made alkaline to pH = 12 by addition of saturated potassium carbonate and extracted with diethylether (2 x 50 mL). The combined organic phase were dried (magnesium sulphate) and evaporated *in vacuo* to give 1-(2-Hydroxy-ethyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester as a clear oil (8.4 g). The protected aminoalcohol was dissolved in dry tetrahydrofuran (150 mL) together with triethylamine (5.6 mL) and cooled to 0 °C under nitrogen. Methanosulfonyl chloride (2.64 mL) in dry THF (30 mL) was added dropwise during 15 min and the mixture was warmed to room temperature and stirred for 30 min. After filtration and concentration *in vacuo* the clear oily residue was dissolved in acetone (300 mL), lithium bromide (14.6 g) was added and the mixture was heated to reflux for 1 h. The mixture was filtered, evaporated *in vacuo* and the product purified by column chromatography on silicagel using as eluent ethyl acetate/heptane (1:1) and fractions containing the product was pooled and evaporated *in vacuo* to give *(RS)-1-(2-Bromo-ethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid-tert-butyl ester* as a clear oil (8 g) which crystallised upon standing.

The following compound was prepared in a similar way:

(RS)-1-(2-Bromo-ethyl)-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid-*tert*-butyl ester

Piperidines of the formula III

The piperidine-derivatives of formula III, wherein X is oxygen, Z is CR^9R^{10}, Y is a bond, A^1, A^2 and A^4 are CH, A^3 is CR^{11}, i.e. spiro[isobenzofuran-1(*3*H),4'-piperidines] are prepared according to the methods described by Marxer et al. *J. Org. Chem.* 1975, *40*, 1427, by Parham et al. *J. Org. Chem.* 1976, *41*, 2628 and by Bauer et al. *J. Med. Chem.* 1976, *19*, 1315.

The following compounds were prepared in a similar way:
6-Fluorospiro[isobenzofuran-1(*3*H),4'-piperidine],
6-trifluoromethylspiro[isobenzofuran-1(*3*H),4'-piperidine],
6-fluoro-3-methylspiro[isobenzofuran-1(*3*H),4'-piperidine],
6-trifluoromethyl-3-methylspiro[isobenzofuran-1(*3*H),4'-piperidine],
5-methylspiro[isobenzofuran-1(*3*H),4'-piperidine],
6-fluoro-3-isobutylspiro[isobenzofuran-1(*3*H),4'-piperidine],
6-fluoro-3-cyclohexylspiro[isobenzofuran-1(*3*H),4'-piperidine] and
6-fluoro-3-(4-fluorophenyl)spiro[isobenzofuran-1(*3*H),4'-piperidine]

The piperidine-derivatives of formula III, wherein X is CR^9R^{10}, Z is NR^8, Y is a bond, A^1, A^2 and A^4 are CH, A^3 is CR^{11} and R^{11} is fluoro or trifluoromethyl, are prepared according to the methods described by Maligres et al. *Tetrahedron* 1997, 53, 10983, and by Cheng et al. *Tet. Lett.* 1997, 38, 1497.

The following compound was prepared in a similar way:
1-Acetyl-5-fluoro-spiro[2,3-dihydro-*1*H-indol-3,4'-piperidine].

The piperidine-derivatives of formula III, wherein the X is CR^9R^{10}, Z is oxygen, Y is a bond, A^1, A^2 and A^4 are CH, A^3 is CR^{11}, i.e. 2,3-dihydro-spiro(benzofuran-3,4'-piperidines), are prepared according to the methods described by Chen, Meng-Hsin; Abraham, John A.

Tetrahedron Lett. **1996**, *37*, 5233-5234 and Slade, P.D. et al. *J. Med. Chem.* **1998**, *41*, 1218-1235.

The following compounds were prepared in a similar way:
2,3-Dihydro-5-fluorospiro[benzofuran-3,4'-piperidine] and
2,3-dihydro-5,6-difluorospiro[benzofuran-3,4'-piperidine]

The substituents R^8 -R^{11} are introduced by applying suitably substituted starting compounds to methods analogous to the above mentioned.

Amines of the formula V

An amine of formula V was prepared by the following procedure:
A mixture of an amine of formula III (1 mmol), (RS)-1-(2-Bromo-ethyl)-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid-*tert*-butyl ester (1.3 mmol) and potassium carbonate (1.3 mmol) in acetonitrile (20 mL) were heated to 85 °C for 6 h. The mixture was cooled to room temperature and evaporated *in vacuo* to give an yellow oily residue. The product was redissolved in dichloromethane (10 mL) and anisole (0.26 mL) and trifluoroacetic acid (10 mL) were added and the mixture stirred at room temperature for 90 min. The mixture was evaporated *in vacuo*. The product was either purified by chromatography or used directly in the next step without purification.

The following compounds were purified by chromatography before further use:

(RS)- 1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-1,2,3,4-tetrahydro-isoquinoline

(RS)-1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-1,2,3,4-tetrahydroisoquinoline

Enantiomeric forms of Amines of the formula V

Enantiomer 1 and enantiomer 2 of N-{4-(3-Fluoro-phenyl)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-piperidin-4-yl}acetamide

Racemic N-{4-(3-fluoro-phenyl)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-piperidin-4-yl}acetamide was subjected to resolution by chiral HPLC using a Gilson SF3 supercritical fluid chromatography system equipped with chiralcelOD columns (4.6 mm x 25 cm for analytical and 10 mm x 25 cm for preparative runs). The particle size in the columns was 10 μm. A solution of the racemic compound N-{4-(3-fluoro-phenyl)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-piperidin-4-yl}acetamide (1 g) in methanol (1 mL) was injected in 40 μL portions on a preparative column. The column was eluted with carbondioxide – modifier (75:25). The modifier was 2-propanol with diethylamine (0.5%) and trifluoracetic acid (0.5%). The flow was 18.9 mL/min at 20 Mpa. Fraction collection was triggered by UV-detection (210 nM). The fractions containing the separate products were pooled and evaporated *in vacuo* which gave the enantiomers. The first eluted enantiomer is called Enantiomer 1 and the second eluted is called Enantiomer 2 of N-{4-(3-fluoro-phenyl)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-piperidin-4-yl}acetamide. The enantiomers were measured by HPLC to have an enantiomeric excess higher than 95%.

The following enantiomers were prepared in a similar way:

Enantiomer 1 and enantiomer 2 of N-{4-(phenyl)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-piperidin-4-yl}acetamide

Examples

Preparation of the compounds of the invention

The compounds of the present invention were prepared by one of two general methods:

Method A: Alkylating a piperidine of formula III with an alkylating derivative of formula II:

A mixture of a piperidine of formula III (1 mmol), (RS)-1-(2-Bromo-ethyl)-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid-*tert*-butyl ester (1.3 mmol) and potassium carbonate (1.3 mmol) in acetonitrile (20 mL) were heated to 85 °C for 6 h. The mixture was cooled to room temperature and evaporated *in vacuo*. The product was purified by chromatography either on silicagel using as eluent ethylacetate/triethylamine (99:1) or by purified by HPLC. Fractions containing the product were pooled and evaporated *in vacuo*.

Method B: Acylating an amine of formula V by the use of a carboxylic acid and a coupling reagent, an activated ester, an acid chloride or an isocyanate:

An amine of formula V (prepared as described above; 1 mmol) and triethylamine (5 mmol) were dissolved in anhydrous acetonitrile (10 mL). An appropriately substituted acid chloride (5 mmol) was added and the reaction mixture stirred at room temperature for 30 min. Methanol (0.5 mL) was added to the reaction mixture followed by evaporation *in vacuo*. The product was purified by chromatography either on silicagel using ethylacetate/triethylamine (99:1) as eluent or by HPLC. Fractions containing the product were pooled and evaporated *in vacuo* and characterised by HPLC-UV-ELSD-MS. The measured HPLC-retention time, the measured molecular mass and UV- and ELSD-purities are shown in **table 1**.

The following compounds were made by the methods indicated in table 1. Analytical data are shown in table 1.

Compound

1. 1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone
2. 1-Cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone
3. 1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid phenethyl-amide
4. 1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-phenylmethanone
5. 1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(2-fluoro-phenyl)methanone
6. 1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-3-phenyl-propan-1-one
7. 1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid (3-chloro-propyl)amide
8. 1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid (2-methoxy-phenyl)amide

9. 1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid tert-butyl ester

10. 3-Chloro-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,2-dimethyl-propan-1-one

12. 1-Cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

13. 1-[2-(4-Chloro-phenoxy)-pyridin-3-yl]-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

14. 1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid tert-butyl ester

15. 1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-phenylmethanone

16. 1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-p-tolylmethanone

17. 1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(2-methoxy-phenyl)methanone

18. 1-Cycloheptyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

19. 1-(2-Fluoro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

20. 1-(2-Chloro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

21. 1-(4-Fluoro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

22. 1-(4-Chloro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

23. 1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid phenethyl amide

24. 1-(1-{2-[6-Fuorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-methoxy-phenyl)methanone

25. 1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-3-phenyl-propan-1-one

26. 2-Ethyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-butan-1-one

27. 1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(3-methoxy-phenyl)methanone

28. 1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-phenylethanone

29. 3-Cyclohexyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-propan-1-one

30. 2-(4-Fluoro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)ethanone

31. 1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid (3,4-dichloro-phenyl)amide

32. 1-Cyclopropyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

33. 1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-pyridin-3-yl-methanone

34. 1-[5-(4-Chloro-phenyl)-2-methyl-furan-3-yl]-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

35. 2-(4-Chloro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)ethanone

36. 1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methyl-propan-1-one

37. 1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid (2-ethyl-phenyl)amide

38. *N*-[1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide

39. 1-Cyclopentyl-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidin-1'-yl]]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

40. 1-Cycloheptyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone

41. N-(1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl)acetamide

42. 1-Cycloheptyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

43. 1-(4-Fluorophenyl)-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

44. 1-Cycloheptyl-1-(1-{2-[5-fluoro-1-methansulfonyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

45. 1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-1-piperidin-1-ylmethanone

46. 1-(4-Fluorophenyl)-1-(1-{2-[5-fluoro-1-methansulfonyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

47. 1-Cycloheptyl-1-(1-{2-[4-(2-methyl-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

48. 1-Cycloheptyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

49. 1-Cyclopentyl-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

50. 1-Cyclopentyl-1-{1-[spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone

51. 1-Cyclopentyl-1-(1-{2-[5-fluoro-1-methansulfonyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

52. 1-(4-Fluorophenyl)-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

53. 1-(2-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

54. 1-Cycloheptyl-1-(1-{2-[spiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

55. 1-Cycloheptyl-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

56. 1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-1-cycloheptylmethanone

57. 1-Cyclopentyl-1-(1-{2-[5-isopropylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

58. N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide

59. 1-Cycloheptyl-1-{1-[2-(4-phenylpiperidin-1-yl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}methanone

60. 1-Cycloheptyl-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

61. 1-Cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

62. 1-Cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

63. 1-(4-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

64. 1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone

65. 1-[1-(2-{2-[1-(4-Fluorophenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenylpiperidin-4-yl]-1-piperidin-1-yl-methanone

66. 1-Cyclopentyl-1-(1-{2-[4-(3-fluoro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

67. 8-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

68. 1-Cycloheptyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

69. 1-[1-(2-{2-[1-(2-Fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenyl-piperidin-4-yl]-1-(4-methyl-piperazin-1-yl)methanone

70. 1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidine-4-carboxylic acid ethyl ester

71. 1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-ethanone

72. 1-Cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

73. 1-Cyclopentyl-1-(1-{2-[4-(2-methyl-1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

74. 1-(1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)ethanone

75. 1-(4-Fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

76. 1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone

77. 1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)-1-(4-fluoro-phenyl)methanone

78. 1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-1-(4-methyl-piperazin-1-yl)methanone

79. 1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-cyclopentylmethanone

80. 1-(4-Fluoro-phenyl)-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

81. 1-(4-Fluorophenyl)-1-(1-{2-[piro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

82. 1-Cyclopentyl-1-(1-{2-[4-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

83. 1-(2-Fluorophenyl)-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

84. N-[4-(3-Fluoro-phenyl)-1-(2-{2-[1-(4-fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-piperidin-4-yl]-acetamide

85. 1-(2-Fluorophenyl)-1-{1-[spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone

86. 1-Cycloheptyl-1-(1-{2-[5-fluoro-1-methansulfonyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

87. 1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-1-piperidin-1-ylmethanone

88. 1-{1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-1-cycloheptylmethanone

89. 1-(2-Fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

90. 1-(1-{2-[(Chloro-trifluoromethyl-phenyl)-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-cycloheptylmethanone

91. 1-(1-{2-[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-cycloheptylmethanone

92. 1-Cycloheptyl-1-(1-{2-[4-(2-isopropoxy-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

93. 1-(1-{2-[4-(7-Chloro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-cyclopentylmethanone

94. 1-Cyclopentyl-1-(1-{2-[4-(2,3-dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

95. 1-(1-{2-[4-(2,3-Dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone

96. N-[1-{2-[2-(1-Cycloheptyl-methanoyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide

97. 1-(4-Fluoro-phenyl)-1-{1-[2-(4-phenyl-piperidin-1-yl)-ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone

98. 1-(1-{2-[4-(6-Chloro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone

99. 1-(4-Fluoro-phenyl)-1-(1-{2-[4-(3-fluoro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

100. 1-Cycloheptyl-1-{1-[spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl}methanone

101. N-(1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide

102. 1-(1-{2-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-1-(2-fluoro-phenyl)methanone

103. 1-cycloheptyl-1-(1-{2-[spiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

104. 1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidine-4-carboxylic acid ethyl ester

105. 1-(1-{2-[4-(4-Dimethylamino-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone

106. 1-Cyclopentyl-1-(1-{2-[4-(4-isopropyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

107. 1-[1-(2-{2-[1-(4-Fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenyl-piperidin-4-yl]ethanone

108. 1-[1-(2-{2-[1-(2-Fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenyl-piperidin-4-yl]ethanone

109. 1-[1-(2-{2-[1-(2-Fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenyl-piperidin-4-yl]-1-piperidin-1-yl-methanone

110. 1-Cyclopentyl-1-{1-[2-(4-phenyl-piperidin-1-yl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}methanone

111. 1-(2-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

112. 1-(4-Fluoro-phenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

113. 1-(4-Fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)methanone

114. 3,3-Dimethyl-[1-{2-[spiro(5-fluor-benzofuran-2*H*-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1*H*-isoquinoline-2-yl]-butan-1-one

115. Cyclohexyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

116. Cyclohexyl-(1-{2-[spiro(5-methyl-isobenzofuran-3*H*-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

117. Cyclohexyl-[1-{2-[spiro(benzofuran-3H-1,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

118. Cyclohexyl-(1-{2-[4-(2-methyl-1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

119. N-{1-[2-(2-Cyclohexanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-4-phenyl-piperidin-4-yl}-acetamide

120. 3,3-Dimethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-butan-1-one

121. Cyclohexyl-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

122. Cyclohexyl-(1-{2-[4-(4-dimethylamino-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

123. 3-Phenyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-propanone

124. (1-{2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-cyclohexyl-methanone

125. 2-Phenoxy-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-ethan-1-one

126. Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

127. Cyclohexyl-(1-{2-[4-(4-isopropyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

128. 2-Propyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-pentan-1-one

129. 2,2-Dimethyl-3-chlor-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-propan-1-one

130. Cyclohexyl-(1-{2-[4-(2,3-dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

131. 3,3-Dimethyl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-butan-1-one

132. Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

133. 2-Ethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-butan-1-one

134. 2-Benzyloxy-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-ethan-1-one

135. Benzo[1,2,5]oxadiazol-5-yl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

136. (1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-cyclohexyl-methanone

137. 1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-3,3-dimethyl-butan-1-one

138. 3,5,5-Trimethyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-hexan-1-one

139. 3,5,5-Trimethyl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-hexan-1-one

140. 2-Phenoxy-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-ethan-1-one

141. (1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-(2,2-dichloro-cyclopropyl)-methanone

142. 2-Benzyloxy-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-ethan-1-one

143. 1-(1-{2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-3,3-dimethyl-butan-1-one

144. 1-(1-{2-[4-(2,3-Dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-3,3-dimethyl-butan-1-one

145. 3,5,5-Trimethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-hexan-1-one

146. 2,2-Dimethyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4--dihydro-1H-isoquinoline-2-yl]-propan-1-one

147. 3-Cyclohexyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

148. Furan-2-yl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

149. N-(4-Phenyl-1-{2-[2-(3,5,5-trimethyl-hexanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)-acetamide

150. Quinoxalin-2-yl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

151. 3-Cyclohexyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-propan-1-one

152. Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[4-(2,3-dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

153. Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[4-(2-methyl-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

154. (Tetrahydro-pyran-4-yl)-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

155. 2-Propyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-pentan-1-one

156. 2-Ethyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-butan-1-one

157. 3-Phenyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

158. 3,3-Dimethyl-1-(1-{2-[4-(2-methyl-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-butan-1-one

159. (1-{2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-(2,2-dichloro-cyclopropyl)-methanone

160. 1,2,3,4-tetrahydro-naphthalene-2-yl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

161. (4-Methylsulfanyl-phenyl)-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

162. 3,5,5-Trimethyl-1-(1-{2-[4-(2-methyl-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-hexan-1-one

163. 3-Phenyl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

164. Furan-2-yl-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

165. 2-Benzyloxy-1-(1-{2-[4-(2-methyl-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

166. 1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-2-phenoxy-ethanone

167. Quinoxalin-2-yl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

168. 2,2-Dimethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

169. (2,2-Dichloro-cyclopropyl)-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

170. 4-Methylsulfanyl-phenyl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

171. . (2,2-Dichloro-cyclopropyl)-(1-{2-[4-(2,3-dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

172. 1-(1-{2-[4-(4-Isopropyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-3,5,5-trimethyl-hexan-1-one

173. 2,2-Dichloro-cyclopropyl-(1-{2-[spiro(isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

174. N-(4-Phenyl-1-{2-[2-(1,2,3,4-tetrahydro-naphthalene-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)-acetamide

175. Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[4-(4-chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

176. N-(1-{2-[2-(3,3-Dimethyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-acetamide

177. 3-Chloro-2,2-dimethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

178. Tetrahydro-pyran-4-yl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-butan-1-one

The following compounds were made as enantiomers by method B starting from Enantiomer 2 of the corresponding amines of formula V. Analytical data are shown in table 1.

Compound

179. N-(4-(3-Fluoro-phenyl)-1-{2-[2-(2-methoxy-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

180. N-(4-(3-Fluoro-phenyl)-1-{2-[2-(2-methoxy-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

181. N-[1-{2-[2-(4-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

182. N-[1-{2-[2-(4-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

183. N-[1-{2-[2-(4-Fluoro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

184. N-(4-(3-Fluoro-phenyl)-1-{2-[2-(4-isopropyl-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

185. N-(4-(3-Fluoro-phenyl)-1-{2-[2-(4-methyl-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

186. N-[1-{2-[2-(3-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

187. N-[1-{2-[2-(2-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

188. N-(1-{2-[2-(4-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

189. N-(1-{2-[2-(2,4-Dichloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

190. N-[1-{2-[2-(2,4-Dichloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

191. N-[1-{2-[2-(Benzo[1,2,5]oxadiazole-5-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

192. N-(4-(3-Fluoro-phenyl)-1-{2-[2-(naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

193. N-[1-[2-(2-Cyclopentanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

194. N-(1-{2-[2-(4-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

195. N-[1-{2-[2-(Benzo[b]thiophene-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

196. N-[1-{2-[2-(6-Fluoro-4H-benzo[1,3]dioxine-8-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]acetamide (Enantiomer)

197. N-[1-{2-[2-(3-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]acetamide (Enantiomer)

198. N-[1-{2-[2-(2-Fluoro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]acetamide (Enantiomer)

199. N-(1-{2-[2-(4-Methyl-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

200. N-[1-{2-[2-(2-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

201. N-(4-(3-Fluoro-phenyl)-1-{2-[2-(4-methoxy-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

202. N-(1-{2-[2-(3-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

203. N-(1-{2-[2-(4-Fluoro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

204. N-{1-[2-(2-Cycloheptanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-4-phenyl-piperidin-4-yl}-acetamide (Enantiomer)

205. N-(1-{2-[2-(3-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

206. 2-N-(4-(3-Fluoro-phenyl)-1-{2-[2-(3-methoxy-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

207. N-(4-(3-Fluoro-phenyl)-1-{2-[2-(thiophene-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

208. N-(4-(3-Fluoro-phenyl)-1-{2-[2-(4-pyrazol-1-yl-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

209. N-(1-{2-[2-(Naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

Table 1. Measured molecular mass ($M+H^+$), measured HPLC-retention time (RT, min) and UV- and ELSD-purities (%) and synthesis method.

compound	$M+H^+$	RT min.	UV-purity (%)	ELSD-purity (%)	Synthesis method
1	500.3	2.34	84.41	100	B
2	474.4	2.38	83.5	100	B
3	496.3	2.45	75.89	100	B
4	481.9	2.29	83.81	100	B

5	500.2	2.29	83.54	100	B
6	510	2.46	84.14	100	B
7	497.4	2.29	100	100	B
8	525.4	2.40	89.67	100	B
9	478.2	2.20	75.37	99.26	A
10	497.1	2.36	75.37	99.26	B
12	463	2.31	100	100	B
13	598.1	2.45	93.85	100	B
14	467	2.43	73.81	96.61	B
15	471.2	2.21	93.09	100	B
16	485	2.34	86.3	100	B
17	501.2	2.27	94.08	100	B
18	491.1	2.54	100	100	B
19	488.9	2.22	84.77	100	B
20	504.9	2.27	77.86	100	B
21	489.2	2.25	80.99	100	B
22	505.1	2.39	85.64	100	B
23	514.2	2.42	79.04	100	B
24	501.3	2.25	83.93	99.53	B
25	499.1	2.42	91.88	100	B
26	465.1	2.34	97.12	100	B
27	501.1	2.25	82.81	100	B
28	485.2	2.27	72.97	100	B
29	505.2	2.73	71.89	100	B
30	502.8	2.31	74.17	100	B
31	554.2	2.60	95.47	100	B
32	435.2	2.06	86.69	100	B
33	472	1.80	95.32	100	B
34	585	2.81	96.53	100	B
35	519	2.44	89.59	100	B
36	437.3	2.13	91.14	100	B
37	514.2	2.40	85.04	100	B
38	520.3	2.29	71.77	76.11	B

39	477.4	2.43	91.78	100	B
40	514.3	2.33	91.25	99.32	B
41	502.3	2.35	70.93	83.59	B
42	551.3	2.44	90.64	100	B
43	503.1	2.37	74.38	100	B
44	550.1	2.50	73.67	95.11	B
45	528.3	2.44	93.37	79.93	B
46	548.2	2.22	94.88	100	B
47	498.3	2.66	74.25	96.35	B
48	513.3	2.77	100	97.34	B
49	537.1	2.33	89.23	100	B
50	486.4	2.12	99.47	100	B
51	522.3	2.29	100	100	B
52	563.1	2.27	72.61	100	B
53	489.2	2.23	76.61	100	B
54	473.6	2.51	70.49	82.63	B
55	565.3	2.55	72.19	100	B
56	479.2	2.74	74.67	83.39	B
57	487.3	2.66	82.69	99.27	B
58	492.2	2.08	85.05	100	B
59	445.5	2.58	70.23	73.14	B
60	505.2	2.65	71.04	76.63	B
61	485.1	2.57	88.72	100	B
62	523.4	2.23	100	100	B
63	549.3	2.19	93.44	100	B
64	502.4	2.29	91.44	100	B
65	554.3	2.38	93.61	100	B
66	435.3	2.38	72.75	93.86	B
67	515.3	2.51	77.67	78.14	B
68	601.3	2.63	81.38	97.64	B
69	569.3	1.65	76.77	88.30	B
70	517.3	2.67	79.03	86.76	B
71	487.4	2.50	72.35	95.17	B

72	573.5	2.42	90.45	100	B
73	470.4	2.45	83.20	100	B
74	459.4	2.27	92.31	100	B
75	599.3	2.36	96.26	98.55	B
76	477.2	2.40	100	93.03	B
77	491.3	2.51	86.66	73.72	B
78	631.5	1.84	75.78	100	B
79	451.1	2.50	86.14	100	B
80	511.1	2.48	100	100	B
81	471.3	2.23	92.66	100	B
82	463.3	2.36	100	100	B
83	563.1	2.24	90.29	100	B
84	518.2	2.03	95.48	100	B
85	512.2	2.02	94.94	88.11	B
86	610.5	2.41	94.60	98.31	B
87	616.2	2.56	89.81	100	B
88	459.3	2.69	71.44	73.94	B
89	599.2	2.33	91.53	100	B
90	623.4	2.65	87.37	98.35	B
91	555.3	2.44	89.31	100	B
92	503.2	2.90	71.70	70.84	B
93	490.2	2.48	100	100	B
94	459.2	2.42	83.29	100	B
95	485.3	2.33	94.29	100	B
96	580.5	2.22	96.44	100	B
97	443.2	2.25	98.80	100	B
98	516	2.42	90.05	100	B
99	461.2	2.29	100	100	B
100	574.4	2.26	99.42	100	B
101	474.4	2.02	100	100	B
102	502.3	2.23	94.60	100	B
103	533.1	2.41	87.36	97.35	B
104	489.4	2.46	79.39	100	B

105	486.4	1.65	88.94	100	B
106	459.5	2.74	81.14	100	B
107	485.4	2.21	94.86	100	B
108	485	2.16	70.08	70.13	B
109	554.4	2.34	70.00	74.91	B
110	417.2	2.35	92.41	100	B
111	549.4	2.14	95.35	100	B
112	507,5	2,45	88.27	98.43	B
113	489.6	2.33	89.20	97.90	B
114	464,6	2,39	97,56	100	B
115	476,6	2,44	97,18	100	B
116	472,7	2,53	98,22	100	B
117	458,6	2,40	86,63	100	B
118	483,7	2,53	99,38	100	B
119	487,7	2,13	95,52	100	B
120	486,6	2,62	94,23	100	B
121	498,6	2,66	98,51	100	B
122	473,7	1,75	94,26	100	B
123	498,6	2,44	97,66	100	A
124	609,1	2,54	97,77	100	B
125	500,6	2,32	93,9	98,82	B
126	508,6	2,37	98,82	100	B
127	472,7	2,83	95,08	100	B
128	492,7	2,63	97,33	100	B
129	485	2,29	94,23	99,4	B
130	472,7	2,52	95,96	100	B
131	460,7	2,49	96,36	100	B
132	534,6	2,48	94,21	99,15	B
133	486,6	2,58	86,65	100	B
134	510,7	2,41	75,55	96,08	B
135	512,6	2,29	98,04	100	B
136	465,1	2,58	96,36	100	B
137	453,1	2,54	97,52	100	B

138	506,7	2,78	98,11	100	B
139	502,7	2,88	77,28	94,4	B
140	496,6	2,39	97,44	100	B
141	491,9	2,44	99,44	99,2	B
142	514,6	2,34	91,48	98,85	B
143	597,1	2,49	97,94	100	B
144	460,7	2,49	95,22	100	B
145	528,7	2,98	98,91	100	B
146	450,6	2,28	100	100	B
147	526,7	2,92	96,57	99,25	B
148	460,5	2,10	96,13	99,34	B
149	517,8	2,50	99,13	100	B
150	522,6	2,26	92,92	99,26	B
151	504,7	2,73	97,79	100	B
152	508,6	2,33	99,37	100	B
153	519,6	2,33	99,06	100	B
154	500,6	2,19	96	99,4	B
155	514,7	2,85	93,87	100	B
156	464,6	2,36	91,14	100	B
157	520,6	2,64	94,34	99,05	B
158	471,7	2,51	97,9	100	B
159	635,9	2,39	96,68	98,58	B
160	520,7	2,69	92,98	99,42	B
161	538,7	2,62	97,24	98,81	B
162	513,8	2,88	95,64	100	B
163	494,7	2,52	98,25	100	B
164	482,5	2,32	91,14	100	B
165	521,7	2,41	93,78	100	B
166	489,1	2,45	97,97	100	B
167	518,7	2,34	87,58	97,31	B
168	472,6	2,50	94,41	99,01	B
169	525,4	2,52	98,4	98,78	B
170	512,7	2,50	98,1	99,2	B

171	499,5	2,37	98,66	99,01	B
172	502,8	3,15	96,92	100	B
173	485,5	2,28	86,08	99,43	B
174	535,7	2,32	89,96	99,01	B
175	501	2,42	98,67	100	B
176	475,7	2,09	97,47	100	B
177	507	2,52	90,73	100	B
178	478,6	1,94	91,92	100	B
179	530,3	2,01	89.59	99.31	B
180	550,2	2,32	96.42	98.14	B
181	534,2	2,15	99.1	100	B
182	578,2	2,18	99.05	100	B
183	518,2	2,00	98.42	99.38	B
184	542,4	2,34	93.23	99.9	B
185	514,4	2,09	99.41	100	B
186	534,2	2,11	98.69	100	B
187	578,3	2,04	71.31	100	B
188	562,2	2,13	95.59	100	A
189	550,2	2,22	88.21	95.21	B
190	568,4	2,22	86.21	98.71	B
191	542,4	2,03	99.09	100	B
192	550,2	2,17	97.37	100	B
193	492,3	2,07	81.75	100	B
194	516,3	2,09	96.4	100	B
195	556,3	2,15	99.36	99.89	B
196	576,3	2,03	96.774	100	B
197	580,4	2,14	98.59	100	B
198	518,2	1,95	82.81	99.74	B
199	496,2	2,15	91.36	99.03	B
200	534,2	2,01	79.14	99.08	B
201	530,3	2,01	99.08	100	B
202	516,3	2,16	94.57	98.33	B
203	500,5	1,97	96.4	100	B

204	502,4	2,25	88.94	100	B
205	562,1	2,20	93.75	96.46	B
206	530,3	2,00	98.7	100	B
207	506,2	1,92	98.2	100	B
208	566,4	1,99	98.45	100	B
209	532,2	2,21	93.74	98.44	B

Pharmacological Testing

The compounds of the invention were tested in a well-recognised and reliable test. The test was as follows:

Inhibition of binding of ^{125}I-NKA to human NK2 receptors

The compounds of the invention have been found to potently inhibit the binding of ^{125}I-NKA to the human NK2 receptor.

By this method, the inhibition by drugs of the binding of ^{125}I-NKA to membranes of human cloned NK2 receptors expressed in CHO-cells is determined *in vitro*.

Briefly, the affinity of the compounds was measured by their ability to displace ^{125}I-NKA, by incubating hNK2 expressing CHO membranes with compound and radioligand at room temperature for 60 minutes. Incubation was terminated by rapid filtration through GF/C filters, and filters were counted in a Wallac Trilux Scintillation Counter. The IC50 values for the compounds No. 1-209, exemplified above, was determined to be 200 nM or less. For the majority of the compounds the IC50 values were 50 nM or less, and for a large group of the compounds the IC50 values were 10 nM or less.

Formulation Examples

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilising the solution and filling it in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets containing 5.0 mg of a compound of the invention calculated as the free base:

Compound **1a** or **1b**	5.0 mg
Lactose	60 mg
Maize starch	30 mg
Hydroxypropylcellulose	2.4 mg
Microcrystalline cellulose	19.2 mg
Croscarmellose Sodium Type A	2.4 mg
Magnesium stearate	0.84 mg

2) Tablets containing 0.5 mg of a compound of the invention calculated as the free base:

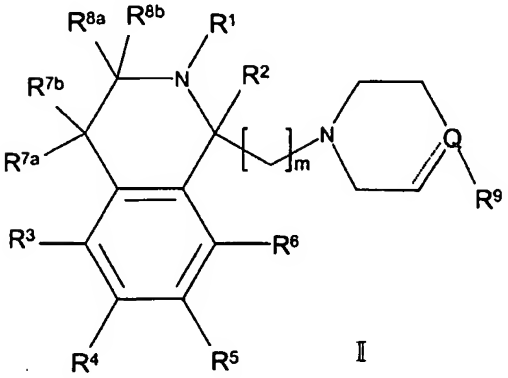
Compound **1a** or **1b**	0.5 mg
Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
Microcrystalline cellulose	14.4 mg
Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

3)	Syrup containing per millilitre:	
	Compound **1a** or **1b**	25 mg
	Sorbitol	500 mg
	Hydroxypropylcellulose	15 mg
	Glycerol	50 mg
	Methyl-paraben	1 mg
	Propyl-paraben	0.1 mg
	Ethanol	0.005 mL
	Flavour	0.05 mg
	Saccharin sodium	0.5 mg
	Water	ad 1 mL

4)	Solution for injection containing per millilitre:	
	Compound **1a** or **1b**	0.5 mg
	Sorbitol	5.1 mg
	Acetic Acid	0.05 mg
	Saccharin sodium	0.5 mg
	Water	ad 1 mL

Patent Claims

1. A 3,4-dihydro-1H-isoquinoloin-2-yl-derivative of formula I



I

wherein

R^1 is a group $R^{11}CO$-, $R^{11}CS$-, $R^{11}SO_2$-, $R^{11}OCO$-, $R^{11}SCO$- or $R^{11}CO$-$CR^{12}R^{13}$- wherein R^{11} is C_{1-12}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl, aryl-C_{1-6}-alkyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, tetrahydropyranyl, 1,2,3,4-tetrahydronaphtalenyl, or 4H-benzo[1,3]dioxinyl optionally substituted with halogen wherein each of said C_{1-6}-alkyl, aryl, heteroaryl and C_{3-8}-cycloalkyl groups independently are unsubstituted or substituted with one or more substituents selected from the group comprising halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, aryl-C_{1-6}-alkoxy, C_{1-6}-alkylsulfanyl, aryl and aryloxy wherein said aryl and aryloxy independently are unsubstituted or substituted with one or more halogen, and R^{12} and R^{13} independently are hydrogen or C_{1-6}-alkyl; or R^1 is a group $R^{14}R^{15}NCO$-, $R^{14}R^{15}NCS$-, wherein R^{14} and R^{15} are independently hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl or aryl-C_{1-6}-alkyl, wherein each of said C_{1-6}-alkyl, aryl and C_{3-8}-cycloalkyl groups independently are unsubstituted or substituted with one or more substituents selected from the group comprising halogen, C_{1-6}-alkyl and C_{1-6}-alkoxy, or R^{14} and R^{15} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepinyl group;

R^2 is selected from hydrogen, trifluoromethyl and C_{1-6}-alkyl;

R^3-R^6, R^{7a}, R^{7b}, R^{8a} and R^{8b} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl;

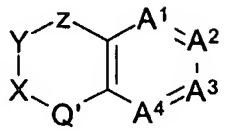
m is 2-6;

R^9 is benzyl, benzoyl, 2,3-dihydrobenzofuranyl or mono- or bicyclic aryl or heteroaryl wherein each benzyl, benzoyl, aryl or heteroaryl optionally is substituted with one or more substituents selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl;

Q is C, N or CR^{10};

wherein R^{10} is selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoromethylsulfonyl, a group $-NR^{30}COR^{31}$ wherein R^{30} is hydrogen or C_{1-6}-alkyl and R^{31} is C_{1-6}-alkyl, a group $-COOR^{16}$ wherein R^{16} is hydrogen or C_{1-6}-alkyl, or a group $-CONR^{17}R^{18}$ wherein R^{17} and R^{18} independently are selected from hydrogen and C_{1-6}-alkyl or R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is unsubstituted or substituted with a C_{1-6}-alkyl;

or R^9 and R^{10} together with the carbon to which they are attached form a cyclic structure selected from the group comprising:



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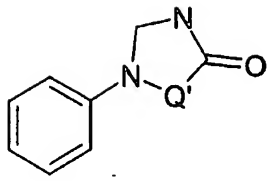
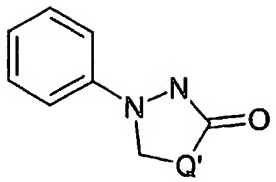
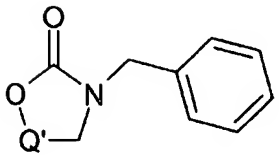


2),



3),



4)

wherein Q' is the carbon shared with the piperidine ring, so that said cyclic structure together with said piperidine ring form a spiro structure; and

X, Y, and Z are independently chosen from O; NR^{19}; $CR^{23}R^{24}$; $S(O)_n$ and a bond; wherein R^{19} is selected from hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, trifluoromethyl, acyl, thioacyl and trifluoromethylsulfonyl, or R^{19} is a group $R^{20}SO_2$-, $R^{20}OCO$- or $R^{20}SCO$- wherein R^{20} is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, or R^{19} is a group $R^{21}R^{22}NCO$- or $R^{21}R^{22}NCS$-, wherein R^{21} and R^{22} are independently hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, or aryl, wherein said aryl is unsubstituted or substituted with one or more substituents selected from C_{1-6}-alkyl or halogen; or R^{21} and R^{22} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepinyl group; R^{23} and R^{24} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl, heteroaryl, wherein said aryl is unsubstituted or substituted with one or more substituents selected from C_{1-6}-alkyl or halogen, amino, C_{1-6}-alkylamino, a group $NR^{25}R^{26}$ wherein R^{25} and R^{26} are independently selected from C_{1-6}-alkyl C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl or R^{25} and R^{26} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl or morpholinyl group, or R^{23} and R^{24} together is

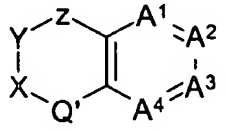
oxo; and n is 0, 1 or 2; provided that no more than one of X, Y and Z may be a bond, and provided that two adjacent groups X, Y or Z may not at the same time be selected from O and S; and

A^1, A^2, A^3 and A^4 are independently selected from N and CR^{27} wherein R^{27} is hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoromethylsulfonyl C_{1-6}-alkylsulfonyl amino or a group $NR^{28}R^{29}$ wherein R^{28} and R^{29} are independently selected from hydrogen and C_{1-6}-alkyl or R^{28} and R^{29} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl or morpholinyl group; provided that only one of A^1, A^2, A^3 and A^4 may be N; and

the dotted line emanating from Q is a bond when Q is C, and no bond when Q is CR^{10} or N;

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1 characterised in that Q is CR^{10}, and R^9 and R^{10} together with the carbon to which they are attached form a bicyclic structure:



1),

wherein Q' is the carbon shared with the piperidine ring, so that said bicyclic structure together with said piperidine ring form a spiro structure; and

X, Y and Z are independently chosen from O; NR^{19}; $CR^{23}R^{24}$ and $S(O)_n$ wherein R^{19} is selected from hydrogen, $C1_{-6}$-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, trifluoromethyl, acyl, thioacyl and trifluoromethylsulfonyl, or R^{19} is a group $R^{20}SO_2$-, $R^{20}OCO$- or $R^{20}SCO$- wherein R^{20} is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, or aryl, or R^{19} is a group

$R^{21}R^{22}NCO$-, $R^{21}R^{22}NCS$-, wherein R^{21} and R^{22} are independently hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, or aryl, wherein said aryl is unsubstituted or substituted with one or more substituents selected from C_{1-6}-alkyl or halogen; or R^{21} and R^{22} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, or perhydroazepinyl group; R^{23} and R^{24} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl, heteroaryl, wherein said aryl is unsubstituted or substituted with one or more substituents selected from C_{1-6}-alkyl or halogen, amino, C_{1-6}-alkylamino, a group $NR^{25}R^{26}$ wherein R^{25} and R^{26} are independently selected from C_{1-6}-alkyl or R^{25} and R^{26} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl, or morpholinyl group, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl or R^{23} and R^{24} together is oxo; and n is 0, 1 or 2; and a bond; provided that no more than one of X, Y and Z may be a bond, and provided that two adjacent groups X, Y or Z may not at the same time be selected from O and S; and

A^1, A^2, A^3 and A^4 are independently selected from N and CR^{27} wherein R^{27} is hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, a group $NR^{28}R^{29}$ wherein R^{28} and R^{29} are independently selected from hydrogen and C_{1-6}-alkyl or R^{28} and R^{29} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl or morpholinyl group, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di- (C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoromethylsulfonyl or C_{1-6}-alkylsulfonyl; provided that only one of A^1, A^2, A^3 and A^4 may be N.

3. A compound according to claim 2 characterised in that X, Y and Z are selected from one of the combinations: X is oxygen, Y is a bond and Z is $CR^{23}R^{24}$; X is $CR^{23}R^{24}$, Y is a bond and Z is oxygen; X is NR^{19}, Y is a bond and Z is $CR^{23}R^{24}$; X is $CR^{23}R^{24}$, Y is a bond and Z is NR^{19}; X is CO, Y is a bond and Z is NR^{19}; X is SO_2, Y is a bond and Z is NR^{19}; X is SO, Y is a bond and Z is NR^{19}; X is $CR^{23}R^{24}$, Y is a bond and Z is S; X is $CR^{23}R^{24}$, Y is a bond and Z is SO; X is $CR^{23}R^{24}$, Y is a bond and Z is SO_2; wherein R^{19} is hydrogen, acetyl

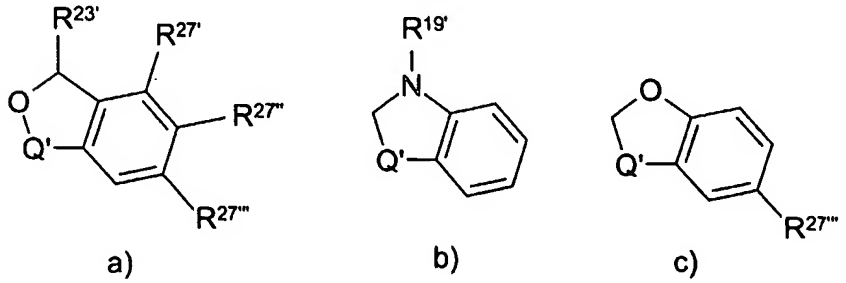
or methylsulfonyl and R^{23} and R^{24} are independently selected from hydrogen, methyl, isobutyl, cyclohexyl and 4-fluorophenyl.

4. A compound according to claim 2 characterised in that -X-Y-Z- together form a group selected from: $-O-CR^{23}R^{24}-$, $-CR^{23}R^{24}-O-$, $-NR^{19}-CR^{23}R^{24}-$, $-CR^{23}R^{24}-NR^{19}-$, $-CO-NR^{19}-$, $-SO_2-NR^{19}-$, $-SO-NR^{19}-$, $-CR^{23}R^{24}-S-$, $-CR^{23}R^{24}-SO-$, $-CR^{23}R^{24}-SO_2-$; wherein R^{19} is hydrogen, acetyl or methylsulfonyl and R^{23} and R^{24} are independently selected from hydrogen, methyl, isobutyl, cyclohexyl and 4-fluorophenyl.

5. A compound according to any of claims 2 to 4 characterised in that A^3 is N or CR^{27} wherein R^{27} is halogen, cyano, nitro, a group $NR^{28}R^{29}$ wherein R^{28} and R^{29} are independently selected from hydrogen and C_{1-6}-alkyl or R^{28} and R^{29} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl, perhydroazepinyl or morpholinyl group, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl, trifluoromethylsulfonyl, or C_{1-6}-alkylsulfonyl.

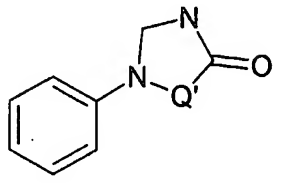
6. A compound according to any of claims 2 to 5 characterised in that A^1, A^2, A^3 and A^4 are independently selected from CR^{27} wherein R^{27} is as defined above.

7. A compound according to claim 2 characterised in that said bicyclic structure is selected from the group comprising:

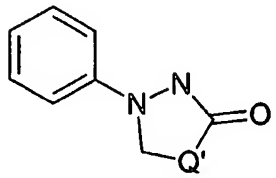


wherein $R^{19'}$ is acetyl or methylsulfonyl, $R^{23'}$ is hydrogen or methyl, $R^{27'}$ is hydrogen or fluoro, $R^{27''}$ is hydrogen, fluoro, methyl or isopropyl, $R^{27'''}$ is hydrogen, fluoro or trifluoromethyl.

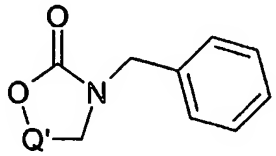
8. A compound according to claim 1 characterised in that R^9 and R^{10} together with the carbon to which they are attached form a cyclic structure selected from the group comprising:



2)



3)



4)

wherein Q' is the carbon shared with the piperidine ring, so that said cyclic structure together with said piperidine ring form a spiro structure.

9. A compound according to claim 1 characterised in that R^9 is benzyl, benzoyl, 2,3-dihydrobenzofuran-7-yl or mono- or bicyclic aryl or heteroaryl wherein each benzyl, benzoyl, aryl or heteroaryl optionally is substituted with one or more substituents selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C1.$_6$-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl.

10. A compound according to claim 9 characterised in that R^9 is 2,3-dihydrobenzofuran-7-yl, benzyl or benzoyl wherein said benzyl or benzoyl is unsubstituted or substituted with one or more halogens in the phenyl groups, or R^9 is mono- or bicyclic aryl or heteroaryl selected from the group comprising phenyl, indolyl, pyridyl, thiophenyl and benzisoxazolyl, wherein each aryl or heteroaryl optionally is substituted with one or more substituents selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C1.$_6$-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl.

11. A compound according to claim 10 characterised in that said mono- or bicyclic aryl or heteroaryl is selected from the group comprising phenyl, indol-3-yl and benzisoxazol-3-yl wherein said phenyl, indol-3-yl or benzisoxazol-3-yl optionally is substituted with one or more substituents selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl.

12. A compound according to claim 11 characterised in that said optional substituents are selected from the group comprising halogen, phenyl and methyl.

13. A compound according to any of claims 9 to 12 characterised in that Q is CR^{10} wherein R^{10} is selected from hydrogen, C_{1-6}-alkylcarbonyl, hydroxy, a group $-NR^{30}COR^{31}$ wherein R^{30} is hydrogen or C_{1-6}-alkyl and R^{31} is C_{1-6}-alkyl, a group $-COOR^{16}$ wherein R^{16} is C_{1-6}-alkyl, or a group $-CONR^{17}R^{18}$ wherein R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is unsubstituted or substituted with a C_{1-6}-alkyl.

14. A compound according to claim 13 characterised in that R^{10} is selected from hydrogen, acetyl, hydroxy, a group $-NR^{30}COR^{31}$ wherein R^{30} is hydrogen and R^{31} is methyl, a group $-COOR^{16}$ wherein R^{16} is ethyl, or a group $-CONR^{17}R^{18}$ wherein R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl or a 4-methylpiperazinyl.

15. A compound according to any of claims 1 to 14 characterised in that m is 2,3 or 4.

16. A compound according to claim 15 characterised in that m is 2.

17. A compound according to any of claims 1 to 16 characterised in that R^1 is a group $R^{11}CO$-, $R^{11}OCO$- wherein R^{11} is C_{3-6}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, phenyl, phenyl-C_{1-6}-alkyl, pyridyl, furanyl, benzo[1,2,5]oxadiazolyl, quinoxalinyl, benzo[b]thiophenyl or naphthalenyl wherein each of said C_{3-6}-alkyl, phenyl, pyridyl and

furanyl groups independently are unsubstituted or substituted with one or more substituents selected from the group comprising halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, phenyl and phenoxy wherein said phenyl and phenoxy independently are unsubstituted or substituted with one halogen; or R^1 is a group $R^{14}R^{15}NCO$-, wherein R^{14} and R^{15} are independently hydrogen, C_{1-6}-alkyl, aryl, or aryl-C_{1-6}-alkyl, wherein each of said C_{1-6}-alkyl and aryl groups independently are unsubstituted or substituted with one substituent selected from the group comprising halogen and C_{1-6}-alkoxy.

18. A compound according to any of claims 1 to 17 characterised in that R^2 is hydrogen.

19. A compound according to any of claims 1 to 18 characterised in that R^3 is hydrogen.

20. A compound according to any of claims 1 to 19 characterised in that R^4 is hydrogen or methoxy.

21. A compound according to any of claims 1 to 20 characterised in that R^5 is hydrogen or methoxy.

22. A compound according to any of claims 1 to 21 characterised in that R^6 is hydrogen.

23. A compound according to any of claims 1 to 22 characterised in that R^{7a} and R^{7b} is hydrogen.

24. A compound according to any of claims 1 to 23 characterised in that R^{8a} and R^{8b} is hydrogen.

25. A compound according to claim 1 characterised in that it is selected from the group comprising:

1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone

1-Cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid phenethyl-amide

1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-phenylmethanone

1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(2-fluoro-phenyl)methanone

1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-3-phenyl-propan-1-one

1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid (3-chloro-propyl)amide

1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid (2-methoxy-phenyl)amide

1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid tert-butyl ester

3-Chloro-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,2-dimethyl-propan-1-one

1-Cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-[2-(4-Chloro-phenoxy)-pyridin-3-yl]-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid tert-butyl ester

1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-phenylmethanone

1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-p-tolylmethanone

1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(2-methoxy-phenyl)methanone

1-Cycloheptyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-(2-Fluoro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-(2-Chloro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-(4-Fluoro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-(4-Chloro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid phenethyl amide

1-(1-{2-[6-Fuorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-methoxy-phenyl)methanone

1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-3-phenyl-propan-1-one

2-Ethyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-butan-1-one

1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(3-methoxy-phenyl)methanone

1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-phenylethanone

3-Cyclohexyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-propan-1-one

2-(4-Fluoro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)ethanone

1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid (3,4-dichloro-phenyl)amide

1-Cyclopropyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-pyridin-3-yl-methanone

1-[5-(4-Chloro-phenyl)-2-methyl-furan-3-yl]-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

2-(4-Chloro-phenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)ethanone

1-(1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methyl-propan-1-one

1-{2-[6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinoline-2-carboxylic acid (2-ethyl-phenyl)amide

N-[1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide

1-Cyclopentyl-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidin-1'-yl]]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-Cycloheptyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone

N-(1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl)acetamide

1-Cycloheptyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-(4-Fluorophenyl)-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-Cycloheptyl-1-(1-{2-[5-fluoro-1-methansulfonyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-1-piperidin-1-ylmethanone

1-(4-Fluorophenyl)-1-(1-{2-[5-fluoro-1-methansulfonyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-Cycloheptyl-1-(1-{2-[4-(2-methyl-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-Cycloheptyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-Cyclopentyl-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-Cyclopentyl-1-{1-[spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone

1-Cyclopentyl-1-(1-{2-[5-fluoro-1-methansulfonyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-(4-Fluorophenyl)-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-(2-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-Cycloheptyl-1-(1-{2-[spiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-Cycloheptyl-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-1-cycloheptylmethanone

1-Cyclopentyl-1-(1-{2-[5-isopropylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide

1-Cycloheptyl-1-{1-[2-(4-phenylpiperidin-1-yl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}methanone

1-Cycloheptyl-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-Cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

1-Cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-(4-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone

1-[1-(2-{2-[1-(4-Fluorophenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenylpiperidin-4-yl]-1-piperidin-1-yl-methanone

1-Cyclopentyl-1-(1-{2-[4-(3-fluoro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

8-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

1-Cycloheptyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-[1-(2-{2-[1-(2-Fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenyl-piperidin-4-yl]-1-(4-methyl-piperazin-1-yl)methanone

1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidine-4-carboxylic acid ethyl ester

1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-ethanone

1-Cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-Cyclopentyl-1-(1-{2-[4-(2-methyl-1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

1-(1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)ethanone

1-(4-Fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone

1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)-1-(4-fluoro-phenyl)methanone

1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-1-(4-methyl-piperazin-1-yl)methanone

1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-cyclopentylmethanone

1-(4-Fluoro-phenyl)-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

1-(4-Fluorophenyl)-1-(1-{2-[piro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-Cyclopentyl-1-(1-{2-[4-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-(2-Fluorophenyl)-1-(1-{2-[6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

N-[4-(3-Fluoro-phenyl)-1-(2-{2-[1-(4-fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-piperidin-4-yl]-acetamide

1-(2-Fluorophenyl)-1-{1-[spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone

1-Cycloheptyl-1-(1-{2-[5-fluoro-1-methansulfonyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-(1-{2-[2-(1-Cycloheptyl-methanoyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-1-piperidin-1-ylmethanone

1-{1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-1-cycloheptylmethanone

1-(2-Fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-(1-{2-[(Chloro-trifluoromethyl-phenyl)-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-cycloheptylmethanone

1-(1-{2-[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-cycloheptylmethanone

1-Cycloheptyl-1-(1-{2-[4-(2-isopropoxy-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

1-(1-{2-[4-(7-Chloro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-cyclopentylmethanone

1-Cyclopentyl-1-(1-{2-[4-(2,3-dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

1-(1-{2-[4-(2,3-Dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone

N-[1-{2-[2-(1-Cycloheptyl-methanoyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide

1-(4-Fluoro-phenyl)-1-{1-[2-(4-phenyl-piperidin-1-yl)-ethyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone

1-(1-{2-[4-(6-Chloro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone

1-(4-Fluoro-phenyl)-1-(1-{2-[4-(3-fluoro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)methanone

1-Cycloheptyl-1-{1-[spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl}methanone

N-(1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide

1-(1-{2-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-1-(2-fluoro-phenyl)methanone

1-cycloheptyl-1-(1-{2-[spiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidine-4-carboxylic acid ethyl ester

1-(1-{2-[4-(4-Dimethylamino-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone

1-Cyclopentyl-1-(1-{2-[4-(4-isopropyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone

1-[1-(2-{2-[1-(4-Fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenyl-piperidin-4-yl]ethanone

1-[1-(2-{2-[1-(2-Fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenyl-piperidin-4-yl]ethanone

1-[1-(2-{2-[1-(2-Fluoro-phenyl)-methanoyl]-1,2,3,4-tetrahydro-isoquinolin-1-yl}-ethyl)-4-phenyl-piperidin-4-yl]-1-piperidin-1-yl-methanone

1-Cyclopentyl-1-{1-[2-(4-phenyl-piperidin-1-yl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}methanone

1-(2-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-6,7-dimethoxy-*1H*-isoquinolin-2-yl)methanone

1-(4-Fluoro-phenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

1-(4-Fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)methanone

3,3-Dimethyl-[1-{2-[spiro(5-fluor-benzofuran-2*H*-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1*H*-isoquinoline-2-yl]-butan-1-one

Cyclohexyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

Cyclohexyl-(1-{2-[spiro(5-methyl-isobenzofuran-3*H*-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

Cyclohexyl-[1-{2-[spiro(benzofuran-3H-1,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

Cyclohexyl-(1-{2-[4-(2-methyl-1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

N-{1-[2-(2-Cyclohexanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-4-phenyl-piperidin-4-yl}-acetamide

3,3-Dimethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-butan-1-one

Cyclohexyl-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

Cyclohexyl-(1-{2-[4-(4-dimethylamino-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

3-Phenyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-propanone

(1-{2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-cyclohexyl-methanone

2-Phenoxy-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-ethan-1-one

Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

Cyclohexyl-(1-{2-[4-(4-isopropyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

2-Propyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-pentan-1-one

2,2-Dimethyl-3-chlor-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-propan-1-one

Cyclohexyl-(1-{2-[4-(2,3-dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

3,3-Dimethyl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-butan-1-one

Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-methanone

2-Ethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-butan-1-one

2-Benzyloxy-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-ethan-1-one

Benzo[1,2,5]oxadiazol-5-yl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)]-ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinolin-2-yl)-cyclohexyl-methanone

1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-3,3-dimethyl-butan-1-one

3,5,5-Trimethyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-hexan-1-one

3,5,5-Trimethyl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-hexan-1-one

2-Phenoxy-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-ethan-1-one

(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-(2,2-dichloro-cyclopropyl)-methanone

2-Benzyloxy-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-ethan-1-one

1-(1-{2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-3,3-dimethyl-butan-1-one

1-(1-{2-[4-(2,3-Dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-3,3-dimethyl-butan-1-one

3,5,5-Trimethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-hexan-1-one

2,2-Dimethyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-propan-1-one

3-Cyclohexyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

Furan-2-yl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

N-(4-Phenyl-1-{2-[2-(3,5,5-trimethyl-hexanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)-acetamide

Quinoxalin-2-yl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-methanone

3-Cyclohexyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-propan-1-one

Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[4-(2,3-dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[4-(2-methyl-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

(Tetrahydro-pyran-4-yl)-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

2-Propyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-pentan-1-one

2-Ethyl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-] ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-butan-1-one

3-Phenyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

3,3-Dimethyl-1-(1-{2-[4-(2-methyl-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-butan-1-one

(1-{2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-(2,2-dichloro-cyclopropyl)-methanone

1,2,3,4-tetrahydro-naphthalene-2-yl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

(4-Methylsulfanyl-phenyl)-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

3,5,5-Trimethyl-1-(1-{2-[4-(2-methyl-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-hexan-1-one

3-Phenyl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

Furan-2-yl-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

2-Benzyloxy-1-(1-{2-[4-(2-methyl-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

1-(1-{2-[4-(4-Chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-2-phenoxy-ethanone

Quinoxalin-2-yl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

2,2-Dimethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

(2,2-Dichloro-cyclopropyl)-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

4-Methylsulfanyl-phenyl-(1-{2-[spiro(5-methyl-isobenzofuran-3H-1,4'-piperidine-1'-yl)]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

(2,2-Dichloro-cyclopropyl)-(1-{2-[4-(2,3-dihydro-benzofuran-7-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

1-(1-{2-[4-(4-Isopropyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-3,5,5-trimethyl-hexan-1-one

2,2-Dichloro-cyclopropyl-(1-{2-[spiro(isobenzofuran-3H-1,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

N-(4-Phenyl-1-{2-[2-(1,2,3,4-tetrahydro-naphthalene-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)-acetamide

Benzo[1,2,5]oxadiazol-5-yl-(1-{2-[4-(4-chloro-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

N-(1-{2-[2-(3,3-Dimethyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)-acetamide

3-Chloro-2,2-dimethyl-1-(1-{2-[4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

Tetrahydro-pyran-4-yl-[1-{2-[spiro(5-fluor-benzofuran-2H-3,4'-piperidine-1'-yl)-]ethyl}-3,4-dihydro-1H-isoquinoline-2-yl]-butan-1-one

1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone,

1-Cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-Chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-Fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-Fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

1-Cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-Fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-Cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro *1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-Fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-Cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone,

1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(cyclopentyl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-(4-Fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-Cyclopentyl-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone,

1-Cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-Fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-Fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

1-Cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl}methanone,

1-(4-Fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl}methanone,

1-Cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro *1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl}methanone,

1-(4-Fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl}methanone,

1-Cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone,

1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-1-(cyclopentyl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-methanone,

1-(4-Fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)-methanone,

1-Cyclopentyl-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-3,4-dihydro-5-fluoro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone,

1-Cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-Fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-Fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

1-Cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-Fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-Cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro *1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-Fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-Cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone,

1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(cyclopentyl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-(4-Fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-Cyclopentyl-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-dichloro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(5-Fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluoro-phenyl)methanone,

1-Cyclopentyl-1-(1-{2-[4-(5-fluoro-*1H*-indol-3-yl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[6-fluorospiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine-1'-yl]ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-Fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluorophenyl)-piperidin-4-yl]acetamide,

N-[1-{2-[2-(1-Cyclopentyl-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

N-[1-{2-[2-(1-(4-Fluorophenyl)-methanoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenylpiperidin-4-yl]acetamide,

1-Cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-Fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-Cyclopentyl-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro *1H*-indol-3,4'-piperidin-1'-yl]-ethyl]-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-(4-Fluorophenyl)-1-{1-[1-acetyl-spiro[2,3-dihydro-5-fluoro-*1H*-indol-3,4'-piperidin-1'-yl]ethyl]-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl}methanone,

1-Cyclopentyl-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(4-Fluorophenyl)-1-(1-{2-[4-(3-trifluoromethylphenyl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(4-fluorophenyl)methanone,

1-(1-{2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-1-(cyclopentyl)methanone,

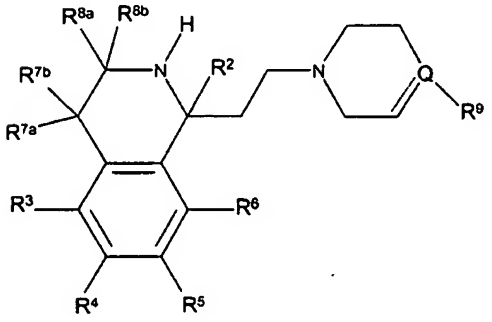
1-(4-Fluorophenyl)-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone,

1-(4-Fluorophenyl)-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone,

1-Cyclopentyl-1-(1-{2-[5,6-difluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone, and

1-Cyclopentyl-1-({2-[6-fluorospiro[benzofuran-1(3H),4'-piperidine-1'-yl]-ethyl}-5,6-difluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)methanone.

or from the group comprising the following enantiomers which are prepared by acylation of Enantiomer 2 of the corresponding amines of formula V,



(V)

wherein R^2-R^9 and Q are as defined for formula I;

and Enantiomer 2 is the slowly eluting of the enantiomer pair by supercritical HPLC at 20 Mpa on a system comprising chiralcelOD columns and an eluent consisting of carbondioxide(75%), 2-propanol(24.75%), diethylamine(0.125%) and trifluoracetic acid(0.125%):

N-(4-(3-Fluoro-phenyl)-1-{2-[2-(2-methoxy-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

N-(4-(3-Fluoro-phenyl)-1-{2-[2-(2-methoxy-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

N-[1-{2-[2-(4-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-[1-{2-[2-(4-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-[1-{2-[2-(4-Fluoro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-(4-(3-Fluoro-phenyl)-1-{2-[2-(4-isopropyl-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

N-(4-(3-Fluoro-phenyl)-1-{2-[2-(4-methyl-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

N-[1-{2-[2-(3-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-[1-{2-[2-(2-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-(1-{2-[2-(4-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

N-(1-{2-[2-(2,4-Dichloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

N-[1-{2-[2-(2,4-Dichloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-[1-{2-[2-(Benzo[1,2,5]oxadiazole-5-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-(4-(3-Fluoro-phenyl)-1-{2-[2-(naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

N-[1-[2-(2-Cyclopentanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-(1-{2-[2-(4-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

N-[1-{2-[2-(Benzo[b]thiophene-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-[1-{2-[2-(6-Fluoro-4H-benzo[1,3]dioxine-8-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]acetamide (Enantiomer)

N-[1-{2-[2-(3-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]acetamide (Enantiomer)

N-[1-{2-[2-(2-Fluoro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]acetamide (Enantiomer)

N-(1-{2-[2-(4-Methyl-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

N-[1-{2-[2-(2-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-(3-fluoro-phenyl)-piperidin-4-yl]-acetamide (Enantiomer)

N-(4-(3-Fluoro-phenyl)-1-{2-[2-(4-methoxy-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

N-(1-{2-[2-(3-Chloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

N-(1-{2-[2-(4-Fluoro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

N-{1-[2-(2-Cycloheptanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-ethyl]-4-phenyl-piperidin-4-yl}-acetamide (Enantiomer)

N-(1-{2-[2-(3-Bromo-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

2-N-(4-(3-Fluoro-phenyl)-1-{2-[2-(3-methoxy-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

N-(4-(3-Fluoro-phenyl)-1-{2-[2-(thiophene-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

N-(4-(3-Fluoro-phenyl)-1-{2-[2-(4-pyrazol-1-yl-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-piperidin-4-yl)acetamide (Enantiomer)

N-(1-{2-[2-(Naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-ethyl}-4-phenyl-piperidin-4-yl)acetamide (Enantiomer)

26. A pharmaceutical composition comprising a compound of any of claims 1 to 25 in a therapeutically effective amount together with one or more pharmaceutically acceptable carriers or diluents.

27. Use of a compound of any of claims 1 to 25 for the manufacture of a pharmaceutical preparation for the treatment of a disorder in the central nervous system.

28. Use according to claim 27 characterised in that the disorder is selected from the group comprising depression, manic depression, bipolar disorder, dysthymia, mixed anxiety depression, generalized anxiety disorder, social anxiety disorder, panic anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, acute stress disorder, phobia, pre-menstrual dysphoric disorder, psychosis and Huntington's disease as well as Parkinson's dementia, adjustment disorders, pain, emesis, migraine, epilepsia, obesity and cerebrovascular disease.

29. Use according to claim 28 characterised in that the disorder is selected from the group comprising depression, manic depression, bipolar disorder, dysthymia, mixed anxiety depression, generalized anxiety disorder, social anxiety disorder, panic anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, acute stress disorder, phobia, pre-menstrual dysphoric disorder and psychosis.

30. Use of a compound of any of claims 1 to 25 in treatment of a disorder in the central nervous system.

31. Use according to claim 30 characterised in that the disorder is selected from the group comprising depression, manic depression, bipolar disorder, dysthymia, mixed anxiety depression, generalised anxiety disorder, social anxiety disorder, panic anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, acute stress disorder, phobia, pre-menstrual dysphoric disorder, psychosis and Huntington's disease as well as Parkinson's dementia, adjustment disorders, pain, emesis, migraine, epilepsia, obesity and cerebrovascular disease.

32. Use according to claim 31 characterised in that the disorder is selected from the group comprising depression, manic depression, bipolar disorder, dysthymia, mixed anxiety depression, generalized anxiety disorder, social anxiety disorder, panic anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, acute stress disorder, phobia, pre-menstrual dysphoric disorder and psychosis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00858

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 409/12, C07D 471/04, C07D 489/04, A61K 31/445, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN-CAPLUS, MEDLINE, EMBASE, EPODOC, BEILSTEIN, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 6465483 B1 (WALTER LÖSEL ET AL), 15 October 2002 (15.10.02), claims 1-15	1-31
A	US 3994891 A (JOHN LAWRENCE HUGHES ET AL), 30 November 1976 (30.11.76), claims 1-13	1-31
A	DE 4104257 A1 (BOEHRINGER INGELHEIM KG), 20 August 1992 (20.08.92), claims 1-29	1-31

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2003	25 -03- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Fernando Farieta/Els Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00858

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 3827727 A1 (BOEHRINGER INGELHEIM KG), 22 February 1990 (22.02.90), claims 1-29	1-31

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INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No.
PCT/DK 02/00858

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INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No.
PCT/DK 02/00858

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		DE 4343641 A	29/06/95
		DE 59409595 D	00/00/00
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00858

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 30-31
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 30-31 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.